CK 01/82/01

NCI/ICRDB/CK01 82/01

PB82-935101

ICRDB CANCERGRAM

CHEMICAL CARCINOGENESIS

Nitroso Compounds

SERIES CK01 No. 82/01

JANUARY, 1982

This Cancergram is a service of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM of the U.S. National Cancer Institute. Every few weeks, an updated Cancergram containing abstracts of selected cancer-related articles recently published in more than 3000 journals, and dealing with the topic indicated by the above title, is sent to researchers working in this area. These researchers are identified on the basis of the description of their current research project that has been submitted to the ICRDB Program, directly or via granting agencies.

This Cancergram is prepared by the Cancer Information Dissemination and Analysis Center (CIDAC) for Carcinogenesis Information. ***If this Cancergram is useful and valuable, please send your comments to the CIDAC address below, since future editions depend on user satisfaction and user needs:***

CIDAC FOR CARCINOGENESIS INFORMATION
SCIENCE INFORMATION SERVICES
FRANKLIN INSTITUTE RESEARCH LABORATORIES
20TH AND RACE STREETS
PHILADELPHIA, PA 19103

NEWARK PUBLIC LIBRARY

FEB 22 1982

U. S. GOVT. PUBS.
DEPOSITORY 376

NEW PUBLICATION SOON TO BE AVAILABLE: RECENT REVIEWS IN CARCINOGENESIS. FOR A SAMPLE COPY, WHILE SUPPLIES LAST, CONTACT: ICRDB PROGRAM, WESTWOOD BLDG., RM. 10A18, BETHESDA, MD. 20205

In this issue:

- FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS..... 1-3
- METABOLISM OF NITROSO COMPOUNDS..... 4-8
- INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS..... 9-21
- MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS..... 22-28
- MUTAGENICITY OF NITROSO COMPOUNDS..... 29-35
- CELLULAR EFFECTS OF NITROSO COMPOUNDS..... 36-42
- IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS..... 43
- EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS..... 44-45
- REVIEWS INCLUDING NITROSO COMPOUNDS..... 46

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20:3173/2:

FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS

1. CHEMISTRY OF N-NITROSAMINES DERIVED FROM ALPHA-AMINO ACIDS.

Polo JS
Simon Fraser University, Burnaby, British Columbia, Canada
Diss Abstr Int (B); 42(1):220-B 1981

In relation to their carcinogenic activity, a series of nitroso derivatives of N-alkyl and N-acyl alpha-amino acids was synthesized and their physical properties as well as their thermal, basic and photolytic decompositions were investigated. (no Refs)

2. SALIVARY LEVELS OF N-NITROSAMINES AND SOME METABOLITES AFTER IP INJECTION OF N-NITROSAMINES IN RATS.

Fliessbach JH, Guttenplan JB
Dept. Biochemistry, New York Univ. Dental Center, New York, NY, 10010
Res Commun Chem Pathol Pharmacol; 33(2):283-291 1981

The carcinogens N-nitrosodimethylamine (DMN) and N-nitrosodiethylamine (DEN) were detected in rat saliva by gas liquid chromatography or HPLC after their ip injections. Salivary levels were equal to or greater than blood levels. A fairly linear dose response in salivary levels was observed in the range of 1-50 mg/kg. Salivary levels of DMN and DEN decreased between 0.5 and 1.0 hr after administration with the decrease becoming more prominent at lower doses. Formaldehyde and bicarbonate, metabolites of DMN, were also detected in rat saliva. (Author abstract) (19 Refs)

3. DIFFERENTIAL PULSE POLAROGRAPHIC DETERMINATION OF BCNU PHARMACOKINETICS IN PATIENTS WITH LUNG CANCER.

Russo R, Bartosek I, Piazza E, Santi AM, Libretti A, Garattini S
(c/o Bartosek), Istituto di Ricerche Farmacologiche 'Mario Negri', Via Eritrea 62, 20157 Milan, Italy
Cancer Treat Rep; 65(7/8):555-562 1981

Carmustine (BCNU) levels were determined by differential pulse polarography in 12 patients with lung cancer. A simple assay method for submicrog quantities of nitrosoureas is described. The half-life of BCNU added to plasma in vitro was 1,413 min at 0 C and 12 min at 37 C during incubation. BCNU kinetics in blood of treated patients was calculated using the two-compartment open model; the half-life of the drug was 1.4 min in the first phase and 17.8 min in the second. Mean distribution vol was 2.59 liters/kg and plasma clearance was 16.7 ml/min/kg. (Author abstract) (15 Refs)

METABOLISM OF NITROSO COMPOUNDS

4. METABOLIC FATE AND CARCINOGENICITY OF N-(OMICRON-HYDROXYALKYL)-N-(4 HYDROXYBUTYL)NITROSAMINES, ANALOGS OF N-BUTYL-N-(4-HYDROXYBUTYL)NITROSAMINE, IN THE RAT.

Suzuki E, Takeda Y, Mochizuki M, Hashimoto Y, Okada M
Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan
Gan; 72(4):539-546 1981

The metabolic fate and carcinogenicity of three omega-hydroxy derivatives of N-alkyl-N-(4-hydroxybutyl)nitrosamines, potent bladder carcinogens, were investigated in the rat. They were N-(2-hydroxyethyl)-N-(4-hydroxybutyl)nitrosamine (HEHBN), N-(3-hydroxypropyl)-N-(4-hydroxybutyl)nitrosamine (HPHBN), and N,N-bis(4-hydroxybutyl)nitrosamine (BHBN). The principal urinary metabolite o HEHBN as well as HPHBN was identified as the corresponding 3-carboxypropyl compound, while the main metabolite of BHBN was N,N-bis(3-carboxypropyl)nitrosamine, indicating the preferential metabolic oxidation of the 4-hydroxybutyl chain to the 3-carboxypropyl group in the N-(omega-hydroxyalkyl)-N-(4-hydroxybutyl)nitrosamines. All three N-nitrosamines having the 4-hydroxybutyl chain induced neither bladder tumor nor any tumor in other organs under conditions similar to those used for N-alkyl-N-(4-hydroxybutyl)nitrosamines. The essential structural and metabolic requirements in N-nitrosamines for the induction of bladder cancer in the rat are discussed. (Author abstract) (25 Refs)

5. METABOLIC FATE OF N-BUTYL-N-(4-HYDROXYBUTYL)NITROSAMINE AND N,N-DIBUTYLNITROSAMINE IN THE GUINEA PIG, WITH REFERENCE TO THEIR CARCINOGENIC EFFECTS ON THE URINARY BLADDER.

Suzuki E, Aoki J, Okada M
Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan
Gan; 72(4):547-551 1981

The metabolic fate of two urinary bladder carcinogens, N-butyl-N-(4-hydroxybutyl)nitrosamine(BBN) and N,N-dibutylnitrosamine (DBN), was studied in the guinea pig, in order to elucidate species differences of response to these N-nitrosamines in this animal species and the rat. Based on the urinary metabolites characterized after oral administration of these compounds, the metabolic pathways of BBN and DBN in the guinea pig were shown to be essentially similar to those in the rat. The principal urinary metabolite of BBN and DBN in the guinea pig, however, was not N-butyl-N-(3-carboxypropyl)nitrosamine (BCPN), as was the case in the rat, but the glucuronic acid conjugate of BBN and that of N-butyl-N-(3-hydroxybutyl)nitrosamine, respectively. The species variation in response to BBN and DBN as bladder carcinogens in these animals is discussed on the basis of the urinary excretion of BCPN. (Author abstract) (27 Refs)

6. METABOLIC FATE OF N,N-DIPROPYLNITROSAMINE AND N,N-DIAMYLNITROSAMINE IN THE RAT, IN RELATION TO THEIR LACK OF CARCINOGENIC EFFECT ON THE URINARY BLADDER.

Suzuki E, Okada M
Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan
Gan; 72(4):552-561 1981

The metabolic fate of N,N-dipropylnitrosamine (DPN) and N,N-dipentyl(=diamyl)nitrosamine (DAN), which induce tumors principally in the liver and esophagus but not in the urinary bladder, was studied in the rat, in order to elucidate the reason for this lack of carcinogenicity to the urinary bladder in contrast with the butyl homolog, N,N-dibutylnitrosamine (DBN), a potent bladder carcinogen. The principal urinary metabolite of DPN was identified as the omega-oxidation product N-propyl-N-(2-carboxyethyl)nitrosamine. The (omega-1)-oxidation product N-propyl-N-(2-hydroxypropyl)nitrosamine and its glucuronic acid conjugate were also characterized as metabolites. The principal urinary metabolite of DAN was N-amyl-N-(2-carboxyethyl)nitrosamine, which was formed by metabolic shortening of the amyl chain by omega- and beta-oxidations according to the Knoop mechanism. Besides this, seven compounds oxidized at omega-, (omega-1)-, (omega-2)-, and (omega-3)-positions of one or both amyl chains were isolated and characterized, some of which were shown to be also present as the corresponding glucuronide. The metabolic pattern of DPN and DAN was compared with that of DBN, and the lack of carcinogenicity of the former N-nitrosamines to the urinary bladder of rats is discussed on the basis of their urinary metabolites. (Author abstract) (20 Refs)

7. URINARY EXCRETION OF N-NITROSODIETHANOLAMINE IN RATS FOLLOWING ITS EPICUTANEOUS AND INTRATRACHEAL ADMINISTRATION AND ITS FORMATION IN VIVO FOLLOWING SKIN APPLICATION OF DIETHANOLAMINE.

Preussmann R, Spiegelhalder B, Eisenbrand G, Wurtele G, Hofmann I
Inst. Toxicology and Chemotherhapy, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Cancer Lett; 13(3):227-231 1981

Urinary excretion of N-nitrosodiethanolamine (NDEA) in male SD rats was measured after treatment of the animals with various doses of the compound. After the epicutaneous administration of 90-184 mg NDEA/animal the mean excretion rate after 24 hr was 73% if the substance was dissolved in water and 79% if it was dissolved in acetone. After intratracheal instillation of 24-38 mg/animal of NDEA, the mean excretion rate after 24 hr was 89%. In a second series of experiments the rats received 2,000 ppm nitrite in their drinking water over a period of 5 days after treatment epicutaneously with single doses of 100, 200, 300 and 400 mg per animal of the parent amine, diethanolamine (DEA). The mean total urinary excretion of NDEA ranged from 2.4-20 ug. Although the rats were treated with relatively high doses of DEA, the in vivo formation of NDEA must be taken into account. It was suggested that human exposure to NDEA might be monitored by the determination of its urinary excretion. (14 Refs)

8. DETERMINANTS OF THE TOXICITY OF L-ALANOSINE TO VARIOUS ORGANS OF THE MOUSE.

Tyagi AK, Thake DC, McGee E, Cooney DA
Lab. Biochemical Pharmacology, Natl. Inst. Arthritis, Metabolism, and, Digestive Diseases NIH, Bethesda, MD, 20205
Toxicology; 21(1):59-69 1981

Male and female BDF1 mice were given 2 ip injections, 1 hr apart, of the antitumor antibiotic L-alanosine (L-2-amino-3-[N-hydroxy,N-nitrosamino]propionic acid). Tissues were assayed for 5-amino-4-imidazole-N-succinocarboxamide ribonucleotide synthetase (SAICAR synthetase), adenylosuccinate synthetase, adenylosuccinate lyase, and L-alanosine and its metabolites. The LD50 of L-alanosine was about 2 g/kg. In general the greatest toxicity occurred in L-5178Y/AR tumor tissue, followed by small intestine, lung, liver, and spleen. The concentration of a antimetabolite of L-alanosine, L-alanosyl-5-amino-4-imidazole carboxylic acid ribonucleotide (L-alanosyl AICOR) correlated with toxicity, supporting the belief that this molecule is responsible for the toxic and therapeutic effects of L-alanosine. Th e correlation is less perfect for SAICAR synthetase, the enzyme which produces L-alanosyl AICOR, because of the effects of adenylosuccinate lyase, which decomposes L-alanosyl-AICOR. Apparently the interaction of the synthesizing enzyme, catabolizing enzyme, and target enzyme determine whether L-alanosyl AICOR occurs in sufficient concentration to cause cellular damage. (13 Refs)

INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS

9. STUDIES ON LUNG TUMOURS. V. SUSCEPTIBILITY OF MICE TO DIMETHYLNITROSAMINE-INDUCED TUMOUR FORMATION IN RELATION TO H-2 HAPLOTYPE.

Den Engelse L, Oomen LC, Van der Valk MA, Hart AA, Dux A, Emmelot P
Div. Chemical Carcinogenesis, The Netherlands Cancer Inst., 1066 CX Amsterdam, The Netherlands
Int J Cancer; 28(2):199-208 1981

Male mice of the strain A/Sn, of its congeneic partner strain A.SW, C57BL/10ScSnA (abbreviated: B10), and of two congeneic strains on a B10 background (B10.A and B10.AKM) were investigated for their susceptibility to lung tumor induction by dimethylnitrosamine (DMN) administered either by ip injection or in the drinking water. Strain B10 (haplotype H-2b) proved to be very resistant, whereas strains A/Sn (H-2b) proved to be very resistant, and strains A/Sn (H-2a) and A.SW (H-2s) were highly susceptible. The introduction of the haplotypes H-2a and H-2m in the resistant strain B10 resulted in a significant increase in sensitivity towards DMN-induced lung tumor formation. Lung tumor incidences in male (B10.A x B10)F1 hybrids, receiving DMN in drinking water, were found to be intermediate between, and significantly different from, the incidences of identically-treated parent strains B10.A and B10. Males of back-cross (B10.A x B10) x B10 BC1 proved to be of low susceptibility to lung tumor formation by DMN, tumor incidence being very low and not significantly different from that observed in identically-treated B10 males. It is concluded that, at least in the model system of B10-derived congeneic strains, H-2 haplotype is one of the factors important in determining susceptibility towards DMN-induced lung tumors. Comparisons of C3Hf (H-2k), C3H/Sn (H-2k) and the latter's

congeneic strains C3H.B10 (H-2b) and C3H.NB (H-2p) of male mice showed that these strains were moderately susceptible to both lung tumor and hepatoma formation by DMN. Accordingly, the presence of an H-2 haplotype from a lung-tumor-resistant strain (H-2b, B10) on the background of a strain of intermediate susceptibility (C3H) does not decrease susceptibility to lung tumor formation. The results were considered in the light of the H-2 haplotype dependence of spontaneous lung tumors, and consequently attention has been paid to the histological types of the induced and spontaneous lung tumors. (Author abstract) (17 Refs)

10. CAPILLARY EMBOLIZATION: PART 2: OCCLUSION OF THE ENTIRE ARTERIAL SYSTEM OF EXPER IMENTALLY INDUCED RENAL TUMORS.

Richter G, Rohrbach R, Kauffman GW, Rassweiler J
Abteilung Rontgendiagnostik, Zentrum Radiologie, Hugstetter Str. 55, 7800 Freiburg, W. Germany
ROEFO; 135(1):85-97 1981

A total of 500 female Wistar rats were deprived of protein and treated with dimethylnitrosamine (60mg/kg body wt). Of these 225 survived the latency period and 221 developed bilateral renal tumors. Tumors were embolized with Ethibloc (E), isobutyl-2-cyanoacrylate (IBC) mixed with Lipidiol Ultrafluid (1:1 mixture), or Gelfoam powder suspended in Urografin (1 g powder/ 30 ml Urografin), using a catheter. Treatment with glucose-controlled Ethibloc produced occlusion of tumor arteries and peripheral vessels. Necrosis occurred in 86% of all tumors up to 6 times normal kidney size, and in 55% of all larger tumors. IBC/Lipidiol treatment did not reach the tumor periphery in all animals. Collateral arterial supply to tumors was intact. Necrosis occurred in 80% of the smaller and 46% of the larger tumors. Gelfoam powder embolization did not effectively reach the peripheral circulation. Necrosis occurred in 64% of the smaller and 11% of the larger tumors. Ligature of the blood supply produced necrosis in only 17% of the smaller and none of the larger tumors. Recurrence and survival rate of tumors was dependent on the stage of tumor development, the effective circulation of the embolization medium, and the vol-dependent embolization. Tumors were shown to be supplied by the main renal artery and by parasitic collateral vessels. Ethibloc proved the most effective medium, with the fewest complications. (66 Refs) (In GER)

11. RENAL TUMORS IN RATS TREATED WITH DIMETHYLNITROSAMINE AND/OR N-ETHYL-N-HYDROXYETHYLNITROSAMINE.

Kitahori Y, Ohshima M, Hiasa Y
First Dept. Pathology, Nara Medical Univ., Nara, Japan
Nara Igaku Zasshi; 32(2):181-188 1981

Male Wistar rats (4-5 wk old) were divided into seven groups; each group of rats were given one or both of two chemicals (dimethylnitrosamine, DMN, or N-ethyl-N-Hydroxyethylnitrosamine, NENH) mixed with standard food pellets during the first 2 wk of the experiment and then were given a stock diet wk 3-36. Group 1 was fed 400 ppm DMN for wk 1 and a basal diet for wk 2; Group 2 was fed 400 ppm DMN wk 1 and 2; Group 3 was fed 100 ppm NEHN wk 1 and the basal diet wk 2; Group 4 was fed 1000 ppm NEHN wk 1 and 2; Group 5 was fed 400 DMN wk 1 and 1000 ppm NEHN wk 2; Group 6 was fed 1000 ppm NEHN wk 1 and 400 ppm DMN wk 2; Group 7 was fed the basal diet wk 1 and 2. Embryonal cell tumors were observed in 33% of the Group 1 rats, 85% of the Group 2 rats, and 8% of the Group 6 rats; no embryonal cell tumors were observed in the Group 5 rats. Renal cell tumors were observed in 16% the Group 1 rats, 7% of the Group 2 rats, 38% of the Group 3 rats, 58% of the Group 4 rats, 33% of the Group 6 rats, and 30% of the Group 5 rats. (33 Refs) (In JPN)

12. THE ROLE OF N-NITROSAMINE IN CARCINOGENESIS AT THE URETEROCOLIC ANASTOMOSIS.

Stewart M, Hill MJ, Pugh RC, Williams JP
St. Paul's Hosp., 24 Endell St., London WC2H 9AE, England
Br J Urol; 53(2):115-118 1981

Seven cases of colonic tumors occurring at the ureterocolic anastomosis (UCA) in patients diverted for benign disease are presented and comparisons made with existing literature. There appears to be a definite increase in the incidence of colonic malignancy in patients with this diversion. A theory of carcinogenesis involving bacterial activation of endogenously formed N-nitrosamine is suggested. Preliminary results of rectal urine analysis support this theory in that high concentrations of N-nitrosamine have been found and mutagens demonstrated. (Author abstract) (10 Refs)

13. THE EFFECT OF N-NITROSO-2-METHOXY-2,6-DIMETHYL-MORPHOLINE ON ENDOCRINE AND EXOCRINE PANCREAS OF SYRIAN HAMSTERS.

Pour PM, Wallcave L, Nagel D
Toxicology Dept., Sandox AG, CH-4133 Pratteln 4, Switzerland
Cancer Lett; 13(3):233-240 1981

N-nitroso-2-methoxy-2,6-dimethylmorpholine (MeNDMM) was administered to groups of male and female (usually five of each sex) 8-wk-old Syrian hamsters. Four concentrations (mg/kg body wt) were used: Group I, 250; Group II, 500; Group III, 1,000; and Group IV, 2,000 All animals of Group IV and three of Group III died during the first 2 wk after treatment. The cause of death in Group IV was diabetic coma. Neoplasms were found in 25/27 hamsters; the two tumor-free hamsters were males from Group I. The number of tumors/female animal increased with the dose of MeNDMM; in the males the number of tumors was 3.4-4.0 in the first three groups. All animals of Group III had developed at least one neoplasm in the liver. In terms of tumors in the stomach, gallbladder, and common duct, female hamsters generally developed more tumors than males. Regarding renal tumor, the males were affected more in Groups I + II; in Group III the difference was not significant. Somewhat like streptozotocin, to which it is structurally related, MeNDMM has been shown to have an almost selective cytotoxic effect on pancreatic beta cells after a single high dose in Syrian hamsters. However, contrary to streptozotocin, MeDNMM appears to have an affinity for both endocrine and exocrine pancreatic tissue. (13 Refs)

14. CHANGES OF AMYLASE DURING EXPERIMENTAL PANCREATIC CARCINOGENESIS IN HAMSTERS.

Takahashi M, Nagase S, Takahashi M, Kokubo T, Hayashi Y
Dept. Chemistry, Sasaki Inst., Kanda Surugadai 2-2, Chiyoda-ku, Tokyo 101, Japan
Gan; 72(4):615-619 1981

Changes of amylase activity and isozymic pattern in the serum, urine, ascites, pancreas and parotid gland of hamsters during pancreatic carcinogenesis induced by N-nitrosobis(2-oxopropyl)am ine (BOP) were examined. During the early stage of pancreatic carcinogenesis, amylase activity in the urine was greatly increased and the pancreatic type of isozyme in-

creased in the serum and urine, but in the terminal stage, the activity decreased and the isozymic pattern reverted to normal. These alterations of amylase could be due to focal pancreatitis around dysplastic ductules and small carcinoma lesions causing leakage of pancreatic juice. This phenomenon may be of value in diagnosis of the early stage of pancreatic cancer. (Author abstract) (8 Refs)

15. GLUCOSE-6-PHOSPHATE DEHYDROGENASE AND GAMMA-GLUTAMYLTRANSPEPTIDASE ACTIVITIES IN THE LIVER DURING CHEMICALLY INDUCED HEPATOCARCINOGENESIS IN RATS AND MICE.

Kojima S, Hama Y, Kubodera A
Dept. Radiopharmacy, Sch. Pharmaceutical Sciences, Teikyo Univ., Suarashi 1019-1, Sagamiko-machi, Takui-gun, Kanagawa, Japan
Toxicol Appl Pharmacol; 60(1):26-32 1981

Male Donryu rats were divided into three groups. One group was fed a diet containing 0.06% 3'methyl-4-(dimethylamino) azobenzene (3'-Me-DAB). The second group was given 60 ppm diethylnitrosamine (DEN) in drinking water. The third group was a control. Eight-wk-old random-bred ddY mice were divided into three groups. The first was fed 0.05% o-aminoazotoluene (o-AT). The second received 0.06% 3'-Me-DAB. The third was a control. Glucose-6-phosphate dehydrogenase (G-6-PDH) and gamma-glutamyltranspeptidase (g-GTP)activities were measured over a period of wk. The hepatic levels of G-6-PDH and g-GTP increased after the start of 3-Me-DAB, DEN, or o-AT administration, decreased once, and then showed sustained increase. Sodium phenobarbital also raised the level of G-6-PDH in rat livers. The data suggest that induction of increased G-6-PDH levels may be closely related to hepatic g-GTP activity in hepatocarcinogenesis in rats and mice. (31 Refs)

16. METASTASIS FROM THE BRAIN OF TRANSPLANTED N-ETHYL-N-NITROSOUREA-INDUCED CENTRAL NERVOUS SYSTEM TUMORS IN RATS.

Vecht CJ, Van Zwieten MJ, Maat B, Van Bekkum DW
Radiobiological Inst. TNO, 151 Lange Kleiweg, Postbox 5815, 2280 HV Rijswijk, The Netherlands
Eur J Cancer; 17(6):703-710 1981

Two transplantable rat CNS tumors induced by N-ethyl-N-nitrosourea (ENU) were employed to study the mechanisms controlling extracranial metastasis from intracranial tumors. Cells derived from a serially passaged anaplastic astrocytoma and a malignant glioma were injected intracerebrally at doses of 10(4), 10(5) and 10(6) cells per rat (Sprague-Dawley and WAG/Rij rats). As soon as neurological dysfunction appeared, animals were sacrificed and examined histologically for (1) extracerebral outgrowth of the intracerebral tumor, (2) the presence of distant metastases within the CNS and (3) remote metastases outside the CNS. In addition to histology, a bioassay procedure was performed. Metastases were found in cervical lymph nodes (74%), lung (21%) and liver (5%). For both tumor groups, rats with both distant CNS metastases and local extracerebral outgrowth developed remote metastases more frequently (p less than 0.05) than animals with intracerebral growth only. The data indicate that both local extracranial spread due to surgical intervention as well as local and distant invasion of leptomeninges promote extracranial metastatic spread. (Author abstract) (21 Refs)

17. EFFECT OF AGE AT TREATMENT ON THE INCIDENCE AND LOCATION OF NEUROGENIC TUMORS INDUCED IN WISTAR RATS BY A SINGLE DOSE OF N-ETHYL-N-NITROSOUREA.

Naito M, Naito Y, Ito A
Dept. Cancer Res., Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi 1-2-3, Minami-ku, Hiroshima 734, Japan
Gan; 72(4):569-577 1981

The effect of age at treatment on the incidence and location of neurogenic tumors induced by N-ethyl-N-nitrosourea (ENU) was investigated in 232 Wistar rats of both sexes. Rats were given 40 mg/kg of ENU on the 16th days of gestation (Group I), on the day of birth (Group II), and on the 1st wk (Group III), 2nd wk (Group IV), 3rd wk (Group V) and 4th wk (Group VI) after birth. Up to 6 mo of observation, the brain consistently showed the highest susceptibility ranging from Group I (93%) to Group VI (36%), followed by the spinal cord (Group I, 34%; Group II, 64%; Group III, 43%). However, the trigeminal nerve was only susceptible in Group I (27%) and Group II (36%) and the spinal root was susceptible exclusively in Group II (46%). Most of the tumors obtained were oligodendrogliomas or mixed gliomas. Glioependymomas of the spinal cord were predominant only in Group II. The temporal and paraventricular regions and hippocampus were the preferred sites of brain tumors in Groups I and II, but in Groups III and IV frontal tumors were predominant. Mesenchymal tumors of the kidney were also induced, mainly in Groups III (16%) and IV (16%). (Author abstract) (28 Refs)

18. CARCINOGENESIS AND AGING. I. MODIFYING EFFECTS OF AGING ON N-METHYL-N-NITROSOUREA-INDUCED CARCINOGENESIS IN FEMALE RATS.

Anisimov VN
Lab. Experimental Tumors, N. N. Petrov Res. Inst. Oncology, 68, Leningradskaya Str., Pesochny-2, Leningrad, 188646, USSR
Exp Pathol (Jena); 19(2):81-90 1981

Three- or 14-mo-old female rats were injected iv with N-nitroso-N-methylurea (MNU), 50 mg/kg body wt, 2 or 4x/wk. There was a direct correlation between the incidence of mammary carcinomas and MNU doses. Kidney tumors occurred inversely proportional to the dose of the carcinogen. Mammary adenocarcinomas were only observed in young MNU-treated rats. Cervicovaginal malignant tumors were only observed in old MNU-treated rats. The incidence of hematopoietic system tumors was the same in animals of both age groups. Rats treated with MNU showed acceleration of benign spontaneous tumor development. The effect of aging on the initial stage of MNU-induced carcinogenesis is believed to be determined by age-associated changes in the proliferative activity of target tissues. The effect of aging on the further development of carcinogenesis may be caused by age-associated hormonal, metabolic, and immunological shifts. (Author abstract) (42 Refs)

19. PRESERVATION OF GASTRIC GLAND CHARACTER IN TRANSPLANTABLE GASTRIC ADENOCARCINOMA (SG2B) OF RATS.

Kokubo T, Takahashi M, Kurokawa Y, Miyahara M, Furihara C, Matsushima T
Dept. Pathology, Natl. Inst. Hygienic Sciences, Kamiyoga 1-18-1, Setagaya-ku, Tokyo 158, Japan
Gan; 72(4):583-589 1981

The morphological and biochemical characteristics of a transplantable tumor line of rat gastric carcinoma (SG2B), that developed in a Wistar strain rat after treatment with N-methyl-

N'-nitro-N-nitrosoguanidine and then 4-nitroquinoline 1-oxide were examined at the 60th passage. The tumor was serially transplanted into newborn rats by sc and ip routes and has been passed through 60 transplant generations over a 4-yr period. The tumors appeared to be well-differentiated tubular adenocarcinomas throughout successive passages, and at each generation transplants were almost identical to the original gastric adenocarcinoma as judged by light and electron microscopic observation. Ultrastructurally, the neoplastic cells contained abundant free ribosomes and exhibited few mucin granules. The microvilli on the apical cell surface were short and irregularly spaced. Electrophoresis showed that pepsinogens (Pg) 3 and 4 were present but no Pg 1 was detectable at the 60th passage, as was the case in the tissue at the 2nd and 5th passages. The tumor tissue has thus retained the morphological and biochemical character of a pyloric gland type tumor for a long time (over 4 yr) during serial transplantation. (Author abstract) (14 Refs)

20. EXPERIMENTAL COLONIC CANCER IN A DOG.

Kamano T, Kurihara H, Kishino H, Mizukami K, Kidokoro T, Wakabayashi K, Kuwabara N
First Dept. Surgery, Juntendo Univ. Sch. Medicine, Tokyo 113, Japan
Jpn J Surg; 11(3):214-218 1981

The histogenesis, mode of proliferation, and metastatic spread of colonic neoplasm induced in a mongrel dog by anal application of N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) were studied. ENNG suppositories were given continuously for 17 mo (a total of 15.8 g of ENNG was given). Bloody feces were first recorded after 6-mo treatment. After 17-mo treatment, a tumor appeared in the anal margin. The animal developed dyschezia, anorexia, and emaciation. Three mo after termination of ENNG treatment, the dog was sacrificed, and the tissues were subjected to histological examination. There was a thickening of the colonic wall, enlargement of the ileocecal, perigastric and tracheal bifurcation lymph nodes. Histologic e xamination of the colonic tumor showed undifferentiated carcinoma, squamous cell carcinoma, and malignant melanoma. Metastases to the regional and distant lymph nodes, lung, liver and renal glomeruli had the histology of undifferentiated carcinoma. Tumors detected in the stomach had the histology of well differentiated adenocarcinoma and signet ring cell carcinoma. (6 Refs)

21. COMPARATIVE CHEMOTHERAPEUTIC INVESTIGATIONS ON TRANSPLANTED AND AUTOCHTHONOUS ACUTE RAT LEUKEMIAS.

Zeller WJ, Schmahl D
Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
J Cancer Res Clin Oncol; 100(3):239-246 1981

The effect of a clinically established drug combination (vincristine, adriamycin, and cytosine arabinoside) against the transplanted rat leukemia L5222 originally induced by ethylnitrosourea (ENU) was compared with its effect against autochthonous acute rat leukemias, also induced by ENU. BD IX rats were used for the transplantation studies and Wistar rats for the autochthonous leukemia studies. Four initial therapy cycles of the drugs was given to compare the response of both leukemia models. In the transplanted model, four cycles had to be given without interruption, and it was impossible to achieve a remission, despite a median survival time of 33 days corresponding to 230% increase in median life-spans of treated rats over that of untreated controls (ILS). The median survival time of the treated autochthonous leukemias for 70 days, corresponding to 419% ILS. For all 15 treated autochthonous leukemias, complete remission was achieved with a median duration of 43 days. The difference in response of these leukemia models is attributed to differences in their kinetics. It is suggested that autochthonous rat leukemias are considerably closer to the human situation than the transplanted rat leukemias. (8 Refs)

MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS

22. EFFECT OF HYPOPHYSECTOMY AND HORMONE REPLACEMENT OF THE GROWTH AND HORMONE RECEPTOR LEVELS OF N-NITROSOMETHYLUREA (NMU)-INDUCED MAMMARY TUMORS IN RATS (MEETING ABSTRACT).

Arafah BM, Manni A, Finegan H, Roe J, Pearson OH
Department of Medicine, Case Western Reserve University, Cleveland, OH, 44106
63rd Annual Meeting of the Endocrine Society, June 17-19, 1981, Cincinnati, Ohio. The Endocrine Society 385 pp., 1981.

Mammary tumors were induced in Sprague-Dawley rats by iv injections of 5 mg/100 g body wt of NMU given 1 wk apart. Hypophysectomy (Hx) induced tumor regression to 49% of the original size in 5 days and to 29% in 15 days in 87% of the tumors (hormone dependent), while the rest remained static or continued to grow. The administration of ovine prolactin (oPRL) (20 IU/day) or estradiol (E2) (2.5 ug bid) for 10 days starting 5 days after Hx prevented further regression of the tumors noted in the untreated group. Simultaneous administration of oPRL and E2 induced reactivation of tumor growth reaching 78% of the original size. Estrogen (ER), progesterone (PgR) and PRL (PRLR) receptors were measured in hormone dependent tumors before and after Hx and after the administration of oPRL and/or E2 using standard techniques. ER level declined in 5 days. Treatment with either oPRL or E2 or both simultaneously had no significant effect on ER levels. The administration of oPRL had no effect on PgR levels while E2 either alone or in combination with oPRL restored PgR to control levels. PRLR declined in 15 days after Hx. Treatment with oPRL or E2 or both simultaneously prevented the decline in PRLR noted in the untreated group. We conclude that growth of NMU-induced rat mammary tumors is dependent on both PRL and E2. There is a synergistic effect between PRL and E2 on tumor growth but not on receptor levels. Neither E2 nor oPRL has any effect on ER levels whereas either one alone or in combination maintains PRLR. PgR is under E2 control and is unaffected by oPRL. (no Refs)

23. EFFECT OF HIGH DOSE ESTROGEN ADMINISTRATION ON THE GROWTH AND PROLACTIN RECEPTOR CONTENT OF THE N-NITROSOMETHYLUREA-INDUCED RAT MAMMARY TUMOR (MEETING ABSTRACT).

Manni A, Rainieri J, Arafah BM, Pearson OH
Department of Medicine, Case Western Reserve University, Cleveland, OH, 44106
63rd Annual Meeting of the Endocrine Society, June 17-19, 1981, Cincinnati, Ohio. The Endocrine Society 385 pp., 1981.

In order to gain further insight into the estrogen vs prolactin dependency of the N-nitrosomethylurea (NMU) mammary

cancer we have investigated the effects of high dose estrogens on the growth and prolactin receptor (PRLR) content of this model. We have also studied whether any effect high dose estrogens might have, could be counteracted by perphenazine (Pz) which stimulates endogenous prolactin release. Daily im injections of 50 ug of estradiol benzoate (E2-B) for 8 days to tumor bearing rats induced marked reduction in tumor size which was already apparent and significant after only 3 injections. Simultaneous daily administration of 1 mg of Pz counteracted the inhibitory effect on tumor growth of E2-B but only partially since the tumors grew significantly more when Pz was injected alone. PRLR content in the tumors was not significantly affected by E2-B treatment. PRLR content was also not significantly different from control in the tumors of rats treated with E2-B+Pz and Pz alone. PRLR were also similar in regressing, static and growing tumors within each group of rats. In addition E2-B treatment did not affect PRLR in the liver membranes. We conclude that administration of pharmacologic doses of estrogens has a potent antitumor action on the NMU-induced rat mammary tumor. This effect can only partially be explained by inhibition of peri pheral action of prolactin. (no Refs)

24. PITUITARY CONTROL OF NITROSOMETHYLUREA-INDUCED RAT MAMMARY TUMOR GROWTH (MEETING ABSTRACT).

Pruitt BT, Rose DP

Wisconsin Clinical Cancer Center, Madison, WI, 53792

63rd Annual Meeting of the Endocrine Society, June 17-19, 1981, Cincinnati, Ohio. The Endocrine Society 385 pp., 1981.

Twenty-four Sprague-Dawley female rats bearing 41 mammary carcinomas induced with N-nitrosomethylurea (NMU) were randomly divided among 3 treatment groups. Group I were ovariectomized and then 2 wk later implanted subcutaneously with silastic capsules containing 17 beta-estradiol 40 mg; after another 2 wk they were treated with hypophysectomy, estradiol implants remaining in place; after a further 2 wk they were killed and samples taken for serum prolactin and tumor progesterone receptor (PgR) assays. Group II were also ovariectomized and implanted with estradiol but were killed after 2 wk of estrogen treatment rather than being hypophysectomized. Group III were treated with ovariectomy alone and were killed 2 wk later. All tumors in Groups I and II increased 50% or more during estrogen treatment. After hypophysectomy, most (13/15) of the tumors in Group I remained static or regressed. For the tumors in Group I shown to be hormone-dependent by 50% or greater response to ovariectomy, the reduction in size after hypophysectomy was significant. However, the PgR levels after hypophysectomy remained as high as the PgR of tumors treated with estrogen alone. These observations suggest that estradiol has a direct effect on NMU-induced mammary carcinomas in stimulating PgR, but that estrogen stimulation of tumor growth is mediated by the pituitary gland. In a related experiment, 10 intact Sprague-Dawley female rats with 10 NMU-induced mammary tumors were treated for 3 wk with bromergocryptine 0.8 mg BID. Although serum prolactin in these rats fell significantly compared with untreated tumor-bearing controls, all tumors continued to grow. Thus, while NMU tumors are apparently dependent on the pituitary for growth, they are not solely dependent on prolactin. (no Refs)

25. EFFECTS OF RESERPINE ON SOME BIOLOGICAL CHARACTERISTICS OF N-NITROSOMETHYLUREA-INDUCED RAT MAMMARY TUMORS (MEETING ABSTRACT).

Verdeal K, Rose DP

Wisconsin Clinical Cancer Center, University of Wisconsin, Madison, WI, 53792

63rd Annual Meeting of the Endocrine Society, June 17-19, 1981, Cincinnati, Ohio. The Endocrine Society 385 pp., 1981.

Reserpine administration influences some chemically-induced rodent mammary tumors by causing hyperprolactinemia. We studied the effect of this drug on carcinomas induced in female Sprague-Dawley rats by different doses of N-nitrosomethylurea (NMU) given on 3 occasions 4 wk apart. In one experiment, reserpine, 50 ug/100 g body wt, was given on the day before, with, and on the day after eac h NMU injection. Tumor peroxidase (p ox) in untreated controls was unaffected by the estrous cycle or NMU dose. Uterine p ox was generally higher at proestrus and estrus than at metestrus and diestrus. Uterine p ox in reserpine-treated rats, in whom diestrus was prolonged, was reduced compared with controls exposed to the same NMU doses. In contrast, the tumor p ox levels in reserpine-treated animals were higher than in the controls, as were the levels of estrogen receptor (ER) and progesterone receptor (PgR). A second experiment was performed in which rats were exposed to 3 injections of NMU, 5 mg/100 g. Reserpine, 50 ug/100 g, was given only with the 2nd and 3rd injections, but then continued daily at 20 ug/100 g starting 1 wk after the last NMU injection. This reserpine treatment schedule resulted in carcinomas with a higher degree of anaplasia than the controls, and there was a strong positive correlation between the tumor ER and p ox levels, both of which were elevated. We conclude that reserpine increases the level of functional ER in NMU-induced mammary carcinomas, as judged by corresponding elevations in PgR and p ox activity. (no Refs)

26. MODIFICATION OF LUNG TUMOR DEVELOPMENT IN A/J MICE.

Witschi HP, Hakkinen PJ, Kehrer JP

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Toxicology; 21(1):37-45 1981

Male and female A/J mice (age 6-8 wk) were divided into five groups with controls. The first group received 500 mg/kg urethan ip. One wk later weekly injections of 300 mg/kg butylated hydroxytoluene (BHT), 500, 300, or 150 mg/kg butylated hydroxyanisole (BHA), or 1,000 mg/kg vitamin E began. The second group received either 10 mg/kg 3-methylcholanthrene (3-MC), 2 injections 1 wk apart, or 7 mg/kg dimethylnitrosamine (DMN), given once. After 1 wk 4 weekly injections of 300 mg/kg BHT were begun. The third group received 500 mg/kg urethan ip, followed after 1 wk by 80 mg/kg methylcyclopentadienyl manganese tricarbonyl (MMT). The fourth group received 400 mg/kg BHT, followed immediately by either a single injection of urethan or a continuous exposure to urethan. The last group received 400 mg/kg BHT followed after 2 wk by either 1,000 or 500 mg/kg urethan. The results show that BHT enhances the development of tumors induced by urethan, 3-MC, or DMN. BHA and vitamin E did not have this effect. MMT produced cell proliferation, but did not enhance carcinogenesis. Apparently the antioxidant property of BHT was not related to effect on tumor development. Rapidly dividing lung cells were not more susceptible to tumor development than resting lung cells. (21 Refs)

27. PROMOTIVE EFFECTS OF DEOXYCHOLIC ACID ON HEPATOCARCINOGENESIS INITIATED BY DIETHYLNITROSAMINE IN MALE RATS.

Cameron R, Imaida K, Ito N

First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, M izuho-ku, Nagoya 467, Japan

Gan; 72(4):635-636 1981

The ability of deoxycholic acid (DA), administered over a short time period, to promote the appearance of hyperplastic foci or hyperplastic nodules in diethylnitrosamine (DEN)-initiated male Fischer rats was examined. The 80 rats were divided into five groups, 15 rats in Groups 1-4 and 20 rats in Group 5. Groups 1, 3, and 5 were injected ip with DEN and later Groups 1 and 3 were fed 0.5% DA or 0.05% phenobarbital (PB), respectively, for 10 wk. Groups 2 and 4 were given saline in place of DEN and later fed DA or PB alone for 10 wk. Both DA and PB (Groups 1 and 3) promoted the development of considerable numbers of foci positive for gamma-glutamyl transferase if preceded by DEN initiation. DEN alone (Group 5) induced much fewer and relatively small foci but induced no hyperplastic nodules. Significantly more and larger foci and a considerably greater number of hyperplastic nodules were seen with DA (Group 1) than with PB (Group 3). DA without DEN (Group 2) induced a small number of foci and hyperplastic nodules. These data suggested that DA is a moderately strong promoter of preneoplastic liver lesions in the male rat. (9 Refs)

28. INHIBITION OF THE FORMATION OF ELECTRICAL CELL COUPLING OF FL CELLS BY TUMOR PROMOTERS.

Enomoto T, Sasaki Y, Shiba Y, Kanno Y, Yamasaki H

Dept. Physiology, Hiroshima Univ. Sch. Dentistry, 2-3, Kasumi 1-chome, Minami-ku, Hiroshima 734, Japan

Gan; 72(4):631-634 1981

The effect of tumor promoters on the formation of electrical cell coupling between human FL cells was investigated by means of a microelectrode technique. In culture medium containing 100 ng/ml of 12-O-tetradecanoyl phorbol-13-acetate (TPA), only 6% of the cells were coupled after 24 hr while more than 90% of the cells were coupled in control medium. The formation of cell coupling was also inhibited by other tumor promoters, phorbol-12,13-didecanoate, ingenol-13,20-dibenzoate and mezerein, whereas non-promoting derivatives, phorbol and 4gamma-phorbol-12,13-didecanoate did not affect cell coupling formation. 7,12-Dimethylbenz[gamma]anthracene, benzo[gamma]pyrene and N-methyl-N'-nitro-N-nitrosoguanidine did not affect the cell coupling. None of the chemicals used changed any electrical properties of the cell membrane, such as membrane potential and membrane resistance, of FL cells. Thus, it appears that TPA and other related tumor promoters inhibit the formation of cell coupling without changing the physiological properties of the membrane significantly. (Author abstract) (16 Refs)

MUTAGENICITY OF NITROSO COMPOUNDS

29. NITRITE CONVERTS 2-AMINO-ALPHA-CARBOLINE, AN INDIRECT MUTAGEN, INTO 2-HYDROXY-ALPHA-CARBOLINE, A NON-MUTAGEN, AND 2-HYDROXY-3-NITROSO-ALPHA-CARBOLINE, A DIRECT MUTAGEN.

Tsuda M, Nagao M, Hirayama T, Sugimura T

Epidemiology Div., Natl. Cancer Center Res. Inst., 5-1-1 Tsukiji, Chuo-ku, Tokyo 104, Japan

Mutat Res; 83(1):61-68 1981

The conversion of 2-amino-alpha-carboline (AAC), a mutagen isolated from the pyrolysate of soybean globulin, into a non-mutagenic hydroxy derivative and then into a new mutagen by treatment with nitrite under acidic conditions is reported. AAC was mutagenic to Salmonella typhimurium in the presence of a rat-liver microsomal fraction (S9 mix): 25 nanomoles of AAC induced 1,156 and 108 revertants of TA98 and TA100, respectively, with S9 mix, and no revertants without S9 mix. Incubation with nitrite under acidic conditions decreased or abolished the mutagenicity with S9 mix. However, below pH 3, mutagenicity that did not require S9 mix appeared. This direct acting mutagen was found to be 2-hydroxy-3-nitroso-alpha-carboline (HNAC) by mass and proton magnetic resonance spectroscopy. It was shown that AAC was converted into 2-hydroxy-alpha-carboline which was then converted into HNAC. The physiological significance of these findings are discussed. (30 Refs)

30. MUTAGENICITY AND RAT-LIVER S9 DEMETHYLATION KINETICS OF N-NITROSOMETHYLANILINE AND ITS RING-SUBSTITUTED DERIVATIVES.

Kroeger-Koepke MB, Andrews AW, Kupper RJ, Koepke SR, Michejda CJ

Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701

Mutat Res; 89(4):255-267 1981

Mutagenicity of N-nitrosomethylaniline (NMA) and its ring-substituted derivatives was investigated using Ames Salmonella typhimurium tester strains. The standard assay involved the application of NMA to strain TA100 (most sensitive toward substituted NMAs) at concentrations ranging from 1-1,000 ug/plate. Neither the parent NMA nor most of its substitutes showed any effect on the tested strains. The same was true in both the presence or absence of Aroclor 1254-induced Sprague-Dawley rat liver S9. In order to test possible activation o: deactivation of the metabolites, the protein concentration of S9 was varied from 0.2 mg/plate to 6.4 mg/plate. The series also included a liquid suspension variant of the Ames assay using all Ames strains. In both test series (various protein concentrations and liquid suspension) the nonmutagenicity of NMA was confirmed. Some ring-substituted derivatives, however, showed a positive mutagenic response (for example, p-NO2, m-Br, m-NO2). (17 Refs)

31. MUTAGENICITY OF N-ALKYL-N-(ALPHA-ACETOXYALKYL)NITROSAMINES IN V79 CHINESE HAMSTER CELLS IN RELATION TO ALKYLATING ACTIVITY.

Huang GF, Mochizuki M, Anjo T, Okada M
Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan
Gan; 72(4):531-538 1981

Mutation to ouabain resistance and cytotoxicity were tested in V79 Chinese hamster cells after the cells had been treated for 2.5 hr with a series of N,N-dialkylnitrosamines (alkyl=methyl, ethyl, propyl, butyl or tert-butyl) monosubstituted at the alpha-carbon with an acetoxy group. The effects of the length of alkyl chain and the mode of substitution with the acetoxy group on the cytoxicity and mutagenicity were examined. In the series of N-alkyl-N-(acetoxymethyl)nitrosamines with an acetoxy group at the primary alpha-carbon, the methylating compound N-methyl-N-(acetoxymethyl)nitrosamine was the most cytotoxic and mutagenic, and the biological activities decreased in the order of ethyl, butyl and propyl homologs. N-tert-Butyl-N-(acetoxymethyl)nitrosamine was not mutagenic at the concentration tested. At equitoxic concentration, N-ethyl-N-(acetoxymethyl)nitrosamine was found to be the most mutagenic. Of the two N-alkyl-N-(alpha-acetoxybutyl)nitrosamines having an acetoxy group at the secondary alpha-carbon, N-methyl-N-(alpha-acetoxybutyl)nitrosamine was more cytotoxic and mutagenic than N-butyl-N-(alpha-acetoxybutyl)nitrosamine. A comparison of the corresponding N-alkyl-N-(acetoxymethyl)nitrosamines and N-alkyl-N-(alpha-acetoxybutyl)nitrosamines showed that the latter had stronger activities. A plot of the mutation frequency versus the ability of the alpha-acetoxy compounds to alkylate 4-(p-nitrobenzyl)pyridine was linear. This indicates that the chemical reactivity of the compounds plays an important role in inducing mutation in V79 Chinese hamster cells. (Author abstract) (26 Refs)

32. EFFECTS OF METABOLIC INHIBITORS ON CELL LETHALITY AND MUTATION INDUCTION IN CHINESE HAMSTER CELLS. II. THE EFFECT OF POSTTREATMENT WITH NON-TOXIC CONCENTRATIONS OF THYMIDINE.

Brennand J, McMillan S, Fox M
Paterson Lab., Christie Hosp. and Holt Radium Inst., Manchester, M20 9BX, England
Chem Biol Interact; 36(1):89-106 1981

The ability of posttreatment exposure to non-toxic concentrations of thymidine (TdR) to enhance the lethal effects of a number of alkylating agents, x-rays and UV and the lethal and mutagenic effects of N-ethyl-N-nitrosourea (ENU) and N-methyl-N-nitrosourea (MNU) has been examined in V79 cell lines. TdR posttreatment enhanced the cytotoxic effects of ethyl methanesulfonate (EMS), MNU and ENU but not of UV or x-rays and increased both the spontaneous and MNU- and ENU-induced frequencies of azaguanine resistant (AzR) mutants. No significant effect of TdR on the spontaneous frequency of thioguanine resistant (TGR) mutants was demonstrated but the frequency of MNU-induced mutants to TGR was enhanced. The effects on expression of both potentially lethal and premutagenic damage were reversed by addition of an equimolar concentration of deoxycytidine (dCdR). The enhancement in spontaneous and induced mutant frequency (IMF) at the HGPRT locus appears to be due to an alteration in the selective efficiency of purine analogues due to alteration in growth kinetics of cells exposed to TdR or treated with alkylated agents or post treatment with thymidine after alkylation damage and not to an alteration in the miscoding potential of alkylated bases. (Author abstract) (17 Refs)

33. THE EFFECTS OF CAFFEINE UPON CELL SURVIVAL AND POSTREPLICATION REPAIR OF DNA AFTER TREATMENT OF BHK 21 CELLS WITH EITHER UV IRRADIATION OR N-METHYL-N-NITROSOGUANIDINE.

Gascoigne EW, Robinson AC, Harris WJ
Dept. Biochemistry, Univ. Aberdeen, Marischal Coll., Aberdeen AB9 1AS, Scotland
Chem Biol Interact; 36(1):107-116 1981

It has been found that in BHK 21 cells caffeine potentiates cell killing by both UV irradiation and N-methyl-N-nitrosoguanidine (MNNG). The potentiating effect is greater with UV than with MNNG. While non-toxic concentrations of caffeine inhibit the joining of newly-replicated DNA fragments into large mol wt DNA (post-replication repair) after UV irradiation, they have no such effect after MNNG treatment. Furthermore, the joining of DNA fragments continues in cells treated with 3 ug/ml of MNNG, a dose which leads to less than 5% cell survival. While inhibition of the synthesis of large mol wt DNA can explain the synergistic effect of caffeine upon cell survival after UV irradiation, it cannot explain the similar effect after MNNG treatment. (Author abstract) (30 Refs)

34. CHARACTERIZATION AND QUANTITATION OF A BALB/C HOST-MEDIATED ASSAY FOR MAMMALIAN CELL TRANSFORMATION BY CHEMICAL CARCINOGENS.

Barnett JW
The University of Texas Graduate School, Galveston, TX
Diss Abstr Int (B); 41(12):4483-B 1981

The peritoneal cavity of the BALB/c mouse was chosen as the depot for the syngeneic BALB/3T3 A31-1-D mammalian cell line to undergo host-mediated chemical exposure. Cells were recovered following four host incubation and the carcinogenic response to chemical agents was monitored by standard in vitro cell transformation bioassay using a focus formation endpoint. Companion in vitro cell transformation assays have also been evaluated by direct application of the same series of carcinogens. Additional experiments were performed to accurately quantify and monitor recovered cell populations to determine the effects of in vivo exposure. Four chemical carcinogens were tested by host-mediated and in vitro transformation assays, and a non-carcinogen, pyrene, tested by host-mediated assay. The direct acting agent ethyl methanesulfonate had positive transforming activity by both assay methods. Two chemicals which require metabolic activation, 2-aminofluorene and dimethylnitrosamine, demonstrated dose-dependent increases in transformation frequencies by host-mediated assay, and were non-transforming by in vitro test. Acrylonitrile, a suspect carcinogen, was positive for host-mediated transformation and negative in the in vitro assay. Pyrene was non-transforming in the in vivo test system. (no Refs)

35. EVIDENCE THAT BENZO(A)PYRENE-RESISTANT, ARYL HYDROCARBON HYDROXYLASE-DEFICIENT VARIANTS OF MOUSE HEPATOMA LINE, HEPA-1, ARE MUTATIONAL IN ORIGIN.

Hankinson O
Lab. Biomedical and Environmental Sciences, Univ. California, Los Angeles, CA, 90024
Somatic Cell Genet; 7(4):373-388 1981

The ability of treatment with known mutagens to increase the frequency of benzo(a)pyrene resistant (BPr) variants was examined. The phenotypic stability of the variants was studied as a function of time in culture and with respect to the degree of heterogeneity among subclones. The in vitro heat lability of the aryl hydrocarbon hydroxylase (AHH) was examined. All strains used were derivatives of the subclone Hepa-1c1c7 of the mouse hepatoma line Hepa-1. Four agents with three distinctly different modes of mutagenic action were used: N-methyl-N'-nitro-N-nitrosoguanidine and ethyl methanesulfonate (alkylating agents), ICR-191G (frame-shift mutagen), and UV light were used. Except for one experiment in which ethyl methanesulfonate only gave a marginal response, the mutagens consistently increased the frequency of BPr clones in a dose-dependent manner. A positive correlation was observed between the frequencies of thioguanine-resistant and BPr clones produced. Many BPr clones possessed considerably reduced, or undetectable AHH activities. Even in those variants that retained considerable AHH activity, heterogeneity in AHH activity among cells of the variants was relatively slight. The sensitivity of BPr variants to the mutagen used for their isolation is described. The in vitro temperature lability of AHH activity in certain BPr variants is discussed. (8 Refs)

CELLULAR EFFECTS OF NITROSO COMPOUNDS

36. O6-ALKYLGUANINE AND STRUCTURAL MODIFICATIONS IN LIVER DNA OF DIALKYLNITROSAMINE-TREATED RATS.

Den Engelse L, Philippus EJ, De Brij RJ
Antoni Van Leeuwenhoek-Huis, Chemical Carcinogenesis Div., Netherland's Cancer Inst., 121, Plesmanlaan, 1066 CX Amsterdam, The Netherlands
Cancer Lett; 13(3):219-225 1981

Experiments are reported on the induction of single-stranded (ss) regions in liver DNA of dimethylnitrosamine (DMN)- or diethylnitrosamine (DEN)-treated rats and its possible relation to the presence or repair of O6-alkylguanine. The Sprague-Dawley female rats were subjected to partial hepatectomy and liver DNA was labeled with (methyl 3H)thymidine. The carcinogens were labeled with (14C). Rats were treated with 1, 10, 20 or 30 mg/kg ip of DMN; 24 hr later the isolated liver was fractionated on benzoylated-naphtholated-diethylaminoethanol cellulose columns. The amount of DNA eluting in the formamide fraction, which contains ss or partially denatured regions, increased in a dose dependent manner (16.2, 21.6, 32.5 and 45.8%, respectively). After 6 days this DNA was reduced to 9.8%, indica ting that the ss and partially denatured regions disappear much more rapidly from rat liver DNA than do those DMN-induced lesions that give rise to more persistent DNA fragmentation in alkaline sucrose gradients. A comparison of the NaCl- and formamide-eluted DNA indicated no significant differences were observed in the extents of alkylation at the O6 and 7-position of guanine. The results indicate, that in the present system, neither the presence nor the repair of O6-alkylguanine is related to the formation of single-stranded regions in rat liver DNA. (13 Refs)

37. INDUCTION OF DNA REPAIR SYNTHESIS IN ISOLATED RAT HEPATOCYTES BY 5-DIAZOURACIL AND OTHER DNA DAMAGING COMPOUNDS.

Andrae U, Schwarz LR
Institut fur Toxikologie und Biochemie, Gesellschaft fur Strahlen- und Umweltforschung, D-8042 Neuherberg, W. Germany
Cancer Lett; 13(3):187-193 1981

The effect of 5-diazouracil (5-DU) on isolated hepatocytes from male Wistar rats (approx 200 g body wt) was studied. It was shown that 5-DU causes DNA damage in rat hepatocytes. DNA repair synthesis was determined by means of the bromodeoxyuridine-CsCl gradient centrifugation method. 5-DU induces DNA repair at concentrations between 20 umol and 500 umol. Radioactivity incorporation was much higher in the presence of 500 uM 5-DU compared with that of 1 mM methylmethanesulfonate or 50 uM N-methyl-N'-nitro-N-nitrosoguanidine. DNA repair was also observed after cell treatment with styrene oxide, benzo[a]pyrene and dimethylnitrosamine. The mechanism by which 5-DU damages DNA is unclear. It is unlikely, however, that oxygenases are involved in the formation of DNA-binding products because 5-DU also induces DNA repair in V79 hamster cells which do not contain detectable monooxygenase activity. (15 Refs)

38. USE OF THE ALKALINE ELUTION TECHNIC TO IDENTIFY DNA DAMAGE CAUSED BY DIMETHYLNITROAMINE (MEETING ABSTRACT).

Pala M, Russo P, Vecchio D, Parodi S, Santi L
Universita Genova, Genoa, Italy
Tumori; 67(2,SupplA):55 1981

The elution profiles of DNA from hepatic nuclei of mice treated with dimethylnitroamine (DMNO) reveal obvious DNA damage. In the body nitroamines are transformed into nitroso derivatives via familiar metabolic pathways; in particular, dimethylnitroamine is transformed into dimethylnitrosamine (DMNA) whose carcinogenic activity and ability to induce DNA damage is known. Dissolved in physiologic solution, the compound was administered to experimental animals (male Swiss CD mice) in single ip injections in doses of 225, 450, and 900 mg/kg. In order to be able to make a comparison between the activities of DMNO and DMNA, the data obtained from administration of DMNA in a dose of 20 mg/kg is also reported. The results are expressed as K (ml (-1)) which is the elution constant (median value). K is inversely proportional to the mol w t of DNA and is essentially a function of the dose of the damaging agent. The values obtained when the animals were sacrificed 4 hr after treatment are as follows: controls K: 0.014; DMNO 225 mg/kg K: 0.031, 450 mg/kg K: 0.051; 900 mg/kg K: 0.080; DMNA 20 mg/kg K: 0.067. In addition to dose dependence, variations in K were also investigated in relation to changes in treatment time with the same dose of DMNO (450 mg/kg). The results were: 2 hr K: 0.028; 4 hr K: 0.051; 6 hr K: 0.033, 24 hr K: 0.029; 48 hr K: 0.029. All of the results are statistically different from the controls. (no Refs) (In ITA)

39. EVALUATION OF DNA DAMAGE INDUCED BY NITROCHLOROBENZENES (MEETING ABSTRACT).

Cesarone CF, Bolognesi C, Santi L
Istituto Scientifico per lo Studio e la Cura dei Tumori, Genoa, Italy
Tumori; 67(2,SupplA):55 1981

It has been shown that the wide range of toxic effects induced by nitrochlorobenzenes in different species of laboratory animals is directly related to the number of chlorine atoms and nitro group substituents and their distribution on the aromatic ring. By means of alkaline elution we have evaluated the damage to liver, kidney, and brain DNA in male Swiss CDI mice after treatment with mono-, di-, and trinitrochlorobenzene in graded doses (1000, 180, 60, mg/kg). All of the tissues examined had significantly greater DNA elutability than the controls. These chemical compounds, however, showed a greater organ tropism for cerebral tissue. In nervous tissue it was discovered that at equally toxic doses the increase in DNA damage was directly proportional to the number of nitro groups present on the molecule. N-nitroso-N-methylurea (NMU), a familiar cerebral carcinogen, was used as a positive control. On the basis of this comparison the damage caused by doses of dinitrochlorobenzene and trinitrochlorobenzene equal to 60 mg/kg is comparable to the damage caused by doses of NMU equal to 100 and 150 mg/kg, respectively. The high specificity of nitrochlorobenzenes for nervous tissue is probably due to its high lipid content which, as in the liver and skin, represents the location of compounds insoluble in water. The concentration of active metabolites of these derivatives in these organs may reach particularly high levels and hence represent a high potential for toxicity. (no Refs) (In ITA)

40. INHIBITORS OF NUCLEAR ADP-RIBOSYL TRANSFERASE RETARD DNA REPAIR AFTER N-METHYL-N-NITROSO-UREA. FURTHER EVIDENCE FOR THE INVOLVEMENT OF (ADP-RIBOSE)N IN DNA REPAIR.

Gray DA, Durkacz BW, Shall S
(c/o Shall) Biochemistry Lab., Biology Building, Univ. Sussex, Brighton, Sussex BN1 9QG, England
FEBS Lett; 131(1):173-177 1981

The rejoining of single-strand breaks in DNA induced by N-methyl-N-nitroso-urea (MNU) was monitored in the presence of transferase inhibitors thymidine and 5-methylnicotinamide using alka line sucrose gradients. DNA in mouse leukemia L1210 cells was labeled with 3H-thymidine. Fractionated acid-insoluble radioactivity was estimated by scintillation spectrometry. Because the combination of 3 milliM deoxycytidine with 10 milliM thymidine had no adverse effect on cell reproduction, this mixture could be used to examine the effect of thymidine on DNA repair after exposure to 1 milliM MNU for 20 min. In the absence of enzyme inhibitors, extensive strand rejoining had occurred by 60 min. In samples containing thymidine or thymidine + cytidine, very little increase in DNA size was observed. 5-methylnicotinamide at 5 milliM also clearly slowed DNA strand rejoining after MNU damage. Two potent inhibitors of ADP-ribosyl transferase were thus shown to retard rejoining of single-strand breaks induced by MNU; further support is given to the conclusion that (ADP-ribose)n participates in DNA repair. (20 Refs)

41. GENOTOXICITY OF N-METHYL-N-NITROSOUREA IN THE PRESENCE OF AMPHOPHILIC MEMBRANE-ACTIVE COMPOUNDS.

Stahl KW, Cheng S-J, Bayer U, Chouroulinkov I
Pathologisches Institut der Universitat Freiburg, 19, Albertstrasse, D-7800 Freiburg, W. Germany
Toxicol Appl Pharmacol; 60(1):16-25 1981

Genotoxicity of N-Methyl-N-nitrosourea (NMU) was measured in vitro in V79 Chinese hamster lung fibroblasts, and in vivo in home-bred Chinese hamsters. NMU was administered in the presence of the sister chromatid marker 5-bromodeoxyuridine (BrdU) and in the presence of the amphophilic, membrane-active compounds n-octanol, Cremophor EL, and 2-(2-methoxyethoxy)ethyl-8-(cis-2-n octylpropyl)octanoate (A2C), according to varying time schedules. Genotoxicity was measured by the occurrence of sister chromatid exchange (SCE). NMU and BrdU together had a significant effect on SCE in vitro that was not detectable in vivo. NMU induced dose-dependent SCE frequencies in V79 cells. Pretreatment of V79 cells with the membrane-active compounds reduced the frequency of NMU-induced SCE. Both cell-integrated and extracellular Cremophor EL reduced NMU genotoxicity. The inhibition effect of Cremophor EL was greater in vivo than in vitro. The results seem to indicate that the amphophilic, membrane-active compounds reduce the genotoxicity of NMU by reducing its bioavailability in the cell nucleus. This is done apparently by increasing the number of nucleophilic sites in the cell membrane, which compete for the NMU molecules. (18 Refs)

42. INTERACTION OF A TRITIUM-LABELED HIGH AFFINITY ANTIESTROGEN (ALPHA-[4-PYRROLIDINOETHOXY] PHENYL-4-HYDROXY-ALPHA-NITROSTILBENE, CI628M) WITH THE MCF-7 HUMAN BREAST CANCER ESTROGEN RECEPTOR (MEETING ABSTRACT).

Eckert RL, Katzenellenbogen BS
Deparment of Physiology and Biophysics, University of Illinois, Urbana, IL, 61801
63rd Annual Meeting of the Endocrine Society, June 17-19, 1981, Cincinnati, Ohio . The Endocrine Society 385 pp., 1981.

These studies examine the binding of a high affinity radiolabeled antiestrogen, [3H] CI628M, to the estrogen receptor from MCF-7 human breast cancer cells. Scatchard analysis indicates a single class of high affinity binding sites with Kd of 1.3 x 10-10M for [3H] estradiol (E2) and 2.2 x 10-10M for [3H] CI628M, and the binding of CI628M and E2 is mutually competitive. Cytoplasmic receptor labeled in vitro with CI628M or E2 sediments as a single 7.7S peak on low salt sucrose gradients. Differences are apparent, however, on high salt gradients where the E2 complex sediments at 4.1S while the CI628M receptor complex sediments as a 4.1S peak with a more rapidly sedimenting shoulder. Likewise, salt extracted 'empty nuclear receptor' labeled in vitro with E2 sediments as a single 4.1S peak while the nuclear receptor sites sediment as two distinct peaks (4.1S, 5.5S) when labeled with CI628M. A similar number of estrogen-competable binding sites are found in each case, however. Following incubation of cells with radiolabeled CI628M or E2 for 1 hr at 37 C, the salt extracted nuclear receptor complexed with E2 sediments at 4.1S (0.4M KCl containing gradients); by contrast, receptor complexed with CI628M sediments as a single peak at 5.5S with a slower sedimenting shoulder. These and related studies indicate that the antiestrogen promoted change in receptor form appears to be associated with exposure to the nuclear compartment. Similar

alteration in receptor properties are observed with another antiestrogen, [3H] trans-hydroxytamoxifen. Hence, antiestrogens may antagonize estrogen action by promoting a change in receptor, or in receptor association with other cellular (possibly nuclear) components; this 'abnormal' receptor may then interact with chromatin acceptor sites in an inappropriate manner, resulting in deficient stimulation of estrogen dependent responses. (no Refs)

IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS

43. RNA ONCOVIRUS EXPRESSION IN N-METHYL-N-NITROSOUREA-INDUCED LYMPHOMAS IN MICE.

Pinter A, Borzsonyi M
Natl. Inst. Hygiene, Budapest, Hungary
Int J Cancer; 28(2):219-223 1981

RNA oncovirus expression was investigated in thymic lymphomas induced by N-methyl-N-nitrosourea (MNU) in (C57BL/6 x DBA/2)F1(BDF1) mice. Out of 15 newborn mice injected with 20 mg/kg MNU, five developed thymic tumors of T-cell origin. Virus production of thymic cells from tumorous and normal animals was studied by an infectious center assay. All five tumors released ecotropic (mouse tropic) virus. No xenotropic or dual-tropic mink cell focus-inducing virus was found. No virus was obtained from thymus cells taken from six normal mice killed between 83 and 124 days; however, an ecotropic virus was cultured from the thymus of a 134-day-old normal mouse. According to these results, the MNU-induced thymic lym phoma development in BDF1 mice is accompanied by activation of endogenous ecotropic virus, whereas spontaneous activation also occurs in older mice. (Author abstract) (23 Refs)

EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS

44. BILE ACIDS IN THE FECES AND THEIR RELATION TO COLON CANCER: COMPARATIVE STUDIES OF JAPANESE AND AMERICANS (MEETING ABSTRACT).

Takahashi M, Kodama M, Tamura T, Ezaki H, Hoshita T, Cohen BI
Dept. Surgery, Chugoku Rosai Hosp., Kure-shi, Hiroshima Pref. 737-01, Japan
Nippon Geka Gakkai Zasshi; 82(Suppl):168 1981

Feces of Japanese and Americans were examined for sterols and iso-bile acids having a hydroxy group at the 3beta position, since the risk of developing colon cancer is greater in Americans than in Japanese. The concentration of bile acid in the feces was 7.5 +-3.4 mg/g of feces for healthy Americans (n=16)and 10.3 +-5.3 mg/g of feces for Americans with colon cancer (n=12). On the other hand, the concentration in the feces of healthy Japanese and those with colon cancer was 2.9 +-1.4 (n=10) and 3.8 +-0.7 mg (n=10), respectively. While the bile of the Americans consisted of only secondary bile acids, that of the healthy Japanese and Japanese with colon cancer was comprised of 33% and 10% primary bile acids, respectively. The percentage of iso-bile acids (isolithocholic acid + isodeoxycholic acid), which are considered to be produced by the intestinal flora, was 33% and 32%, respectively, for the healthy Americans and Americans with colon cancer, while it was 16% and 31%, respectively, for the healthy Japanese and Japanese with colon cancer. When methylnitrosourea (MNU) was injected into the intestines of rats, the percentage of rats which developed colon tumors was 49%, but when MNU was given together with isolithocholic or lithocholic acid, it was 46% and 65%, respectively, only lithocholic acid having a colon cancer-promoting effect. (no Refs) (In JPN)

45. ENDOGENOUS CARCINOGENS.

Hill MJ
Bacterial Metabolism Res. Lab., Central Public Health Lab., London, England
Practitioner; 225(1356):803-804,807-809 1981

Estradiol is a potential endogenous carcinogen. Consuming a high fat/high energy diet, by increasing circulating estrogen levels and estrogen receptor activity, may increase the risk of carcinogenesis in estrogen-dependent tissues (breast, endometrium, possibly ovary). The role of cholesterol in carcinogenesis is not yet clear. The author's studies showed no relationship between fecal cholesterol levels and the risk of intestinal cancer in case-control studies. Some of the numerous urinary metabolites of tryptophan seem to be related to non-industrial bladder cancer. Intestinal bacteria can derive carcinogenic substances (ethionine, phenol, p-cresol, N-nitroso compounds, bile acid metabolites, etc) f rom dietary components and convert exogenous chemicals (eg, polycyclic aromatic hydrocarbons) to proximate carcinogens. It is relatively easy to determine which carcinogens might be produced under ideal conditions, but there is limited information on which carcinogens are actually produced in vivo, and very little information regarding their importance. (27 Refs)

REVIEWS INCLUDING NITROSO COMPOUNDS

46. INDUCTION IN RATS OF LIVER DNA SINGLE-STRAND BREAKS BY THE POLYCHLORINATED BIPHENYL AROCHLOR 1254.

Robbiano L, Pino A
Istituto di Farmacologia dell' Universita di Genova, Genoa, Italy
Boll Soc Ital Biol Sper; 57(4):407-413 1981

Arochlor 1254 (a mixture of polychlorinated biphenyls) induces benign and malignant tumor growth in mice by prolonged administration. Mutagenic and clastogenic studies done so far gave contradictory results. Single doses of Arochlor 1254 (67, 648 or 1,295 mg/kg) given to male albino rats by gastric gavage does max damage in 4-12 hr and almost complete repair is achieved after 48 hr. Daily administration might result in a cumulative effect, because DNA damage is only partially repaired after 24 hr. Arochlor 1254 is 40 times less carcinogenic than diethylnitrosamine and is 110 times less effective in causing DNA damage. (17 Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Andrae U. 37
Andrews AW. 30
Anisimov VN. 18
Anjo T. 31
Aoki J. 5
Arafah BM. 22
Arafah BM. 23
Barnett JW. 34
Bartosek I. 3
Bayer U. 41
Bolognesi C. 39
Borzsonyi M. 43
Brennand J. 32
Cameron R. 27
Cesarone CF. 39
Cheng S-J. 41
Chouroulinkov I. 41
Cohen BI. 44
Cooney DA. 8
De Brij RJ. 36
Den Engelse L. 36
Den Engelse L. 9
Durkacz BW. 40
Dux A. 9
Eckert RL. 42
Eisenbrand G. 7
Emmelot P. 9
Enomoto T. 28
Ezaki H. 44
Finegan H. 22
Fliessbach JH. 2
Fox M. 32
Furihara C. 19
Garattini S. 3
Gascoigne EW. 33
Gray DA. 40
Guttenplan JB. 2
Hakkinen PJ. 26
Hama Y. 15
Hankinson O. 35
Harris WJ. 33
Hart AA. 9
Hashimoto Y. 4
Hayashi Y. 14
Hiasa Y. 11
Hill MJ. 12
Hill MJ. 45
Hirayama T. 29
Hofmann I. 7
Hoshita T. 44
Huang GF. 31
Imaida K. 27
Ito A. 17
Ito N. 27
Kamano T. 20
Kanno Y. 28
Katzenellenboge. 42
Kauffman GW. 10
Kehrer JP. 26
Kidokoro T. 20
Kishino H. 20
Kitahori Y. 11
Kodama M. 44
Koepke SR. 30
Kojima S. 15
Kokubo T. 14
Kokubo T. 19
Kroeger-Koepke. 30
Kubodera A. 15
Kupper RJ. 30
Kurihara H. 20
Kurokawa Y. 19
Kuwabara N. 20
Libretti A. 3
Maat B. 16
Manni A. 22
Manni A. 23
Matsushima T. 19
McGee E. 8
McMillan S. 32
Michejda CJ. 30
Miyahara M. 19
Mizukami K. 20
Mochizuki M. 31
Mochizuki M. 4
Nagao M. 29
Nagase S. 14
Nagel D. 13
Naito M. 17
Naito Y. 17
Ohshima M. 11
Okada M. 31
Okada M. 4
Okada M. 5
Okada M. 6
Oomen LC. 9
Pala M. 38
Parodi S. 38
Pearson OH. 22
Pearson OH. 23
Philippus EJ. 36
Piazza E. 3
Pino A. 46
Pinter A. 43
Polo JS. 1
Pour PM. 13
Preussmann R. 7
Pruitt BT. 24
Pugh RC. 12
Rainieri J. 23
Rassweiler J. 10
Richter G. 10
Robbiano L. 46
Robinson AC. 33
Roe J. 22
Rohrbach R. 10
Rose DP. 24
Rose DP. 25
Russo P. 38
Russo R. 3
Santi AM. 3
Santi L. 38
Santi L. 39
Sasaki Y. 28
Schmahl D. 21
Schwarz LR. 37
Shall S. 40
Shiba Y. 28
Spiegelhalder B. 7
Stahl KW. 41
Stewart M. 12
Sugimura T. 29
Suzuki E. 4
Suzuki E. 5
Suzuki E. 6
Takahashi M. 14
Takahashi M. 14
Takahashi M. 19
Takahashi M. 44
Takeda Y. 4
Tamura T. 44
Thake DC. 8
Tsuda M. 29
Tyagi AK. 8
Van Bekkum DW. 16
Van Zwieten MJ. 16
Van der Valk MA. 9
Vecchio D. 38
Vecht CJ. 16
Verdeal K. 25
Wakabayashi K. 20
Wallcave L. 13
Williams JP. 12
Witschi HP. 26
Wurtele G. 7
Yamasaki H. 28
Zeller WJ. 21

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. THE GENETIC TOXICOLOGY OF ALDRIN AND DIELDRIN.
Ashwood-Smith MJ
Environmental Toxicology Res. Group, Dept. Biology, Univ. Victoria, Victoria, BC V8W 2Y2, Canada
Mutat Res; 86(2):137-154 1981

RADIATION CARCINOGENESIS

2. EFFECTS OF LOW-LEVEL RADIATION ON BIOLOGIC SYSTEMS: A LITERATURE REVIEW.
Best TL, Hoditschek B
Eastern New Mexico Univ., Portales, NM
Effects of Low-Level Radiation on Biologic Systems: A Literature Review. Available from National Technical Information Service, Springfield, VA, as SAND-80-7143:, 246 pp., 1981.

3. PHOTOCARCINOGENESIS: AN OVERVIEW.
Forbes PD
Skin and Cancer Hosp., 3322 North Broad St., Philadelphia, PA, 19140
J Invest Dermatol; 77(1):139-143 1981

DIETARY FACTORS IN CARCINOGENESIS

4. EPIDEMIOLOGICAL CORRELATIONS BETWEEN DIET AND CANCER FREQUENCY.
Correa P
Louisiana State Univ. Medical Center, New Orleans, LA, 70112
Cancer Res; 41(9,part2):3685-3689 1981

5. ROLE OF DIETARY FIBER IN DIVERTICULAR DISEASE AND COLON CANCER.
Talbot JM
Life Sciences Res. Office, Federation of American Societies for Experimental Biology, Bethesda, MD, 20014
Fed Proc; 40(9):2337-2342 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

6. PRIMARY HEPATIC CANCER IN ALCOHOLICS.
Tamburro CH, Lee HM
Liver Res. Center, Div. Digestive Diseases and Nutrition, Univ. Louisville Health Sciences Center, 511 South Floyd St., Louisville, KY, 40232
Clin Gastroenterol; 10(2):457-477 1981

7. PANCREATIC CANCER AND ALCOHOL.
Okuda K, Ohnishi K
Dept. Medicine, Chiba Univ. Sch. Medicine, 1-8-1 Inohana, Chiba City (280), Japan
Clin Gastroenterol; 10(2):479-484 1981

8. HELMINTHS IN THE INDUCTION OF CANCER. II. SCHISTOSOMA HAEMATOBIUM AND BLADDER CANCER.
Schwartz DA
Inst. Medicine, Far Eastern Univ., Manila, Philippines
Trop Geogr Med; 33(1):1-7 1981

9. GENETICS OF WILMS'S TUMOR.
Matsunaga E
Dept. Human Genetics, Natl. Inst. Genetics, Mishima, Shizuoka-Ken, 411, Japan
Hum Genet; 57(3):231-246 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

10. NEOPLASMS: COMPARATIVE PATHOLOGY OF GROWTH IN ANIMALS, PLANTS, AND MAN.
Kaiser HE
Dept. Pathology, Univ. Maryland Sch. Medicine, Baltimore, MD
Neoplasms: Comparative Pathology of Growth in Animals, Plants, and Man. Baltimore, Williams and Wilkins, 908 pp., 1981.

11. PULMONARY CARCINOGENESIS: ARYL HYDROCARBON HYDROXYLASE.
McLemore TL, Martin RR
Dept. Medicine, Baylor Coll. Medicine, Houston, TX, 77030
Cancer Treat Res; 1:1-34 1981

12. THE GENETIC TOXICITY OF HYDROXYLAMINES.
Marfey P, Robinson E
Dept. Biological Sciences, State Univ. New York at Albany, Albany, NY, 12222
Mutat Res; 86(2):155-191 1981

MODIFICATION OF CARCINOGENESIS

13. MODIFYING FACTORS OF CHEMICAL CARCINOGENESIS.
Beliaev II, Litvinov IuA
Medical Inst., Gorki, USSR
Gig Sanit; (6):59-62 1981
In RUS

14. ANTIPROLIFERATIVE EFFECTS OF RETINOIDS RELATED TO THE CELL CYCLE-SPECIFIC INHIBITION OF ORNITHINE DECARBOXYLASE.
Russell DH, Haddox MK
Dept. Pharmacology, Univ. Arizona Coll. Medicine, Tucson, AZ, 85724
Ann NY Acad Sci; 359:281-297 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

15. PATHOGENESIS OF THYMIC LYMPHOMAS IN C57BL MICE.
Boniver J
Laboratoire d'Anatomie Pathologique, Tour de Pathologie B. 23, Universite de Liege au Sart Tilman, 4000 Liege, Belgium
Pathol Res Pract; 171(2):268-278 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

16. CRITICAL ASSESSMENT OF THE VALUE OF IN VITRO CELL TRANSFORMATION FOR PREDICTING IN VIVO CARCINOGENICITY OF CHEMICALS.
Brookes P
(c/o Lohman, P. H.), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 86(2):233-242 1981

OTHER REVIEWS IN CARCINOGENESIS

17. MAMMALIAN GENETICS AND CANCER.
Russell ES
Jackson Lab., Bar Harbor, ME, 04609
Prog Clin Biol Res 45: 327 pp., 1981.

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
5285 Port Royal Road
Springfield, Va. 22161

OFFICIAL BUSINESS

Penalty for Private Use, $300

PRINTED MATTER

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF COMMERCE
COM-211

THIRD CLASS
BULK RATE

U.S.MAIL

CK-01

CANCERGRAMS are distributed for the International Cancer Research Data Bank (ICRDB) by the National Technical Information Service (NTIS). CANCERGRAMS are available from NTIS on a standing order basis at $2 each for North American Continent addressees and $3 each for other addressees. An NTIS deposit account is required. For a list of subject categories or other information, please write to:

Subscription Section
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161

NOTICE OF MAILING CHANGE

☐ Check here if you wish to discontinue receiving this publication.

☐ Check here if your address has changed and you wish to continue receiving this publication. (Be sure to furnish your complete address including zip code.)

Tear off cover with address label still affixed and send to:

Computer Support Center
ICRDB Program
IIT Research Institute
10 West 35th Street
Chicago IL. 60616

CK 01/82/02

NCI/ICRDB/CK01 82/02 PB82-935102

ICRDB CANCERGRAM

CHEMICAL CARCINOGENESIS

Nitroso Compounds

SERIES CK01 No. 82/02 FEBRUARY, 1982

This Cancergram is a service of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM of the U.S. National Cancer Institute. Every few weeks, an updated Cancergram containing abstracts of selected cancer-related articles recently published in more than 3000 journals, and dealing with the topic indicated by the above title, is sent to researchers working in this area. These researchers are identified on the basis of the description of their current research project that has been submitted to the ICRDB Program, directly or via granting agencies.

This Cancergram is prepared by the Cancer Information Dissemination and Analysis Center (CIDAC) for Carcinogenesis Information. ***If this Cancergram is useful and valuable, please send your comments to the CIDAC address below, since future editions depend on user satisfaction and user needs:***

CIDAC FOR CARCINOGENESIS INFORMATION
SCIENCE INFORMATION SERVICES
FRANKLIN INSTITUTE RESEARCH LABORATORIES
20TH AND RACE STREETS
PHILADELPHIA, PA 19103

VISIT THE ICRDB BOOTH DURING THE ASCO/AACR MEETINGS FOR COMPLEMENTARY SEARCHES OF CANCERLINE IN ADDITION TO SAMPLE COPIES OF ICRDB PUBLICATIONS.

In this issue:

- FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS 1-7
- METABOLISM OF NITROSO COMPOUNDS 8
- INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS 9-26
- MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS 27-32
- MUTAGENICITY OF NITROSO COMPOUNDS 33-38
- CELLULAR EFFECTS OF NITROSO COMPOUNDS 39-41
- IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS 42-45
- EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS 46-48
- REVIEWS INCLUDING NITROSO COMPOUNDS 49-50

NEWARK PUBLIC LIBRARY

APR 2 1982

U. S. GOVT. PUBS.
DEPOSITORY 376

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20.3173/2:

FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS

1. GASTRIC JUICE N-NITROSAMINES IN HEALTH AND GASTRODUODENAL DISEASE.

Reed PI, Haines K, Smith PL, House FR, Walters CL
Gastrointestinal Unit, Wexham Park Hosp., Slough, Berkshire SL2 4HL, England
Lancet; 2(8246):550-552 1981

The concentrations of total extractable N-nitroso compounds, pH, and nitrite levels were measured in fasting gastric juice, which was also cultured for bacteria, from 50 healthy volunteers and 217 patients with common upper gastrointestinal complaints. The concentrations of N-nitroso compounds and pH levels rose significantly with age. Sex and cigarette smoking had no significant effect. There was a positive correlation between pH and N-nitroso concentration, and between pH and an increase in the concentration of nitrites. A significant relation was demonstrated between raised N-nitroso and nitrite levels and growth of nitrate reductase-positive microorganisms. These results demonstrate for the first time in man the interrelations of N-nitrosamine concentration, pH, gastric juice nitrite, and nitrate-reducing bacteria. The findings are considered in relation to the risks of development of gastric cancer in man. (Author abstract) (30 Refs)

2. EFFECT OF CIMETIDINE ON GASTRIC JUICE N-NITROSAMINE CONCENTRATION.

Reed PI, Haines K, Smith PL, House FR, Walters CL
Gastrointestinal Unit, Wexham Park Hosp., Slough, Berkshire SL2 4HL, England
Lancet; 2(8246):553-556 1981

Total extractable N-nitroso compounds, pH, and nitrite levels were measured in, and microorganisms were cultured from, the fasting gastric juice of 140 patients taking the H2-receptor antagonist cimetidine and from 267 subjects, including 50 healthy volunteers, not taking cimetidine. Significantly higher mean N-nitrosamine concentrations and pH levels were demonstrated in the cimetidine-treated patients; N-nitrosamine concentration increased with pH. In 30 patients studied, cimetidine treatment significantly increased gastric pH and N-nitrosamine concentrations, while in 23 patients withdrawal of cimetidine treatment resulted in a significant reduction of pH but not of N-nitrosamine concentrations. The gastric juice nitrite level was often raised and nitrate-reducing bacteria cultured were similar to those associated with other causes of hypochlorhydria. These results demonstrate for the first time a relation between gastric juice N-nitrosamine concentration, pH, and cimetidine treatment, and the findings are discussed in relation to gastric cancer induction. (Author abstract) (32 Refs)

3. ABSENCE OF VOLATILE NITROSAMINES IN HUMAN FECES.

Lee L, Archer MC, Bruce WR
(c/o Bruce) Dept. Medical Biophysics, Univ. Toronto, Ontario Cancer Inst., 500 Sherbourne St., Toronto, Ontario, M4X 1K9, Canada
Cancer Res; 41(10):3992-3994 1981

Using a method for nitrosamine analysis that gives high recovery values and that is free from artifactual synthesis of nitrosamines, we have shown that human feces do not contain volatile nitrosamines (detection limit, 0.1 to 0.5 ug/kg). We also showed that nitrosation reactions are not catalyzed by fecal organisms. Following a 2-day anaerobic incubation of feces with either a secondary amine (dimethylamine, dipropylamine, or morpholine) or nitrite, no nitrosamine was formed. When the amine and nitrite were added together, nitrosamine was formed, but at a level of 2 to 20% of that formed in autoclaved feces under the same conditions. Nitrosamines were stable following anaerobic incubation with feces for up to 4 days. These results suggest that fecal organisms inhibit the chemical formation of nitrosamines instead of catalyzing it. When morpholine and nitrate were added together, nitrosomorpholine was formed. Morpholine nitrosates so rapidly that it intercepts nitrite formed by the action of nitrate reductase before the nitrite can be further reduced. However, very high concentrations of morpholine and nitrate, which are far from the conditions in normal feces, were required to form measurable nitrosomorpholine. We may conclude that N-nitroso compounds are unlikely to be formed in any significant amounts in the human colon. (Author abstract) (24 Refs)

4. INHIBITION OF N-NITROSAMINE FORMATION BY SOYA PRODUCTS.

Kurechi T, Kikugawa K, Fukuda S, Hasunuma M
Tokyo Coll. Pharmacy, 1432-1, Horinouchi, Hachioji, Tokyo 192-03, Japan
Food Cosmet Toxicol; 19(4):425-428 1981

The soya products Tofu (soya bean curd), Miso (soya bean paste), soya milk without additives, and Bonlact (powdered soya milk with linoleic acid, vitamins, and minerals added) were tested at pH 3, 4, and 5. Known amounts of the soya products were added to reaction mixtures containing sodium citrate buffer (pH 3 or 4) and NaNO2. All of the products tested reduced the levels of nitrite in the reaction mixtures. Reductions were faster at pH 3 than at pH4 and were dependent on the amount of soya product present. The most potent product was Miso, followed by Bonlact, Tofu, and soya milk, in order. Soya products were added to mixtures of NaNO2 and dimethylamine or NaNO2 and diethylamine. All products inhibited the formation of N-nitrosodimethylamine with greatest inhibition at pH 3. The most potent product was Bonlact, followed in order by Miso, Tofu, and soya milk. The in vitro results suggest that soya products may inhibit the formation of the potential carcinogens, the n-nitrosamines, in the stomach. The component(s) which causes the inhibition is not known. It may be either the unsaturated fatty acid component of the lipids or any of a variety of phenolic compounds. (19 Refs)

5. CHROMATOPOLAROGRAPHY OF N-NITROSAMINES INCLUDING DETERMINATION OF N-NITROSODIETHANOLAMINE IN COSMETIC PRODUCTS.

Vohra SK, Harrington GW
E. G. and G. Princeton Applied Res. Corporation, Princeton, NJ, 08540
Food Cosmet Toxicol; 19(4):485-487 1981

A method combining high-performance liquid chromatography and differential pulse polarography to detect N-nitrosamines in substances such as cosmetics is described. Four classes of N-nitroso compounds were tested: (I) volatile, (II) low-polarity, non-volatile, (III) high-polarity, non-volatile, non-ionic, and (IV) high-polarity, ionic, non-volatile compounds. The most important class III compo und was N-nitrosodiethanolamine (NDELA), a potential contaminant in certain cosmetic products. A variety of cosmetic compounds were analyzed as purchased and after the addition of known amounts of NDELA. Results indicated a sensitivity to less than nanog amounts, with even smaller amounts possibly detectable

with modifications. No NDELA was detected in the cosmetics as purchased. Extraction efficiencies ranged from 44-96%. The variation was attributed to the variety of ingredients in the compounds tested. Results with any one compound were fairly consistent over a range of NDELA concentrations. (14 Refs)

6. ANALYSIS OF VOLATILE N-NITROSAMINES IN COMMERCIAL DRUGS.

Castegnaro M, Pignatelli B, Walker EA
International Agency for Res. on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France
Food Cosmet Toxicol; 19(4):489-491 1981

Gas chromatography using a chemiluminescence detector was used to test drugs containing aminopyrine, disulfiram, or oxytetracycline for contamination with volatile N-nitrosamines. The recovery rates for the method were determined to be 70-90%. Thirty-seven drugs thought possibly to contain n-nitrosamines were analyzed. The aminopyrine- and oxytetracycline-containing drugs were found to contain N-nitrosodimethylamine in amounts ranging from 1 to 900 ug/kg. All four disulfiram compounds contained n-nitrosodiethylamine in amounts ranging from 94 to 980 ug/kg. Within samples of a given drug, variations were observed that were due to variations in the formulation of individual tablets. The possible intake of N-nitrosamines for a person taking oxytetracycline drugs was found to be more than previously-determined intake levels from food and comparable to intake levels from alcoholic beverages. The significance of nitrosamines in drugs to the incidence of cancer in humans is unknown. (15 Refs)

7. NITROSABLE DRUGS.

Ziebarth D
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 51(7):587-595 1981

The nitrosation of 61 potentially nitrosable drugs available for po administration in East Germany was studied in vitro under simulated conditions of the human stomach. Nitrosation of 10/61 drugs (aminophenazone, ampicillin, clomipramine, desipramine, ethambutol, imipramine, noramidopyrine methanesulfonate, oxacillin, phenoxymethylpenicillin, and piperazine) was observed. Nitrosodimethylamine, the principal product of aminophenazone, and mononitrosopiperazine, the principal product of piperazine, were identified chemically among the nitrosation products of the drugs. Both metabolites are carcinogenic for several animal species. The nitrosation of 9/10 drugs were inhibited 80-100% by ascorbic acid, and that of ampicillin by 18.2%. The findings indicate that po administered drugs forming carcinogenic N-nitroso comp ounds should be replaced by non-nitrosable drugs, and other potentially nitrosable drugs should be formulated with ascorbic acid, if they are compatible with this vitamin. (33 Refs) (In GER)

METABOLISM OF NITROSO COMPOUNDS

8. METABOLISM OF CHEMICAL CARCINOGENS BY CULTURED HUMAN AND RAT BLADDER EPITHELIAL CELLS.

Autrup H, Grafstrom RC, Christensen B, Kieler J
Lab. Environmental Carcinogenesis, Copenhagen, Denmark
Carcinogenesis; 2(8):763-768 1981

Cells from human bladder epithelium cell lines HU1689, HU1752, and HU1765 and primary bladder epithelial cells from Wistar rats were exposed in vitro for 24 hr to radioactively-labeled carcinogens dissolved in the medium: [1,3,6-3H]benzo[a]pyrene (BP) 1.5 uM; [G3H]aflatoxin B1 (AFB) 1.5 uM; [14C]N-nitrosodimethylamine (DMNA) 100 uM; [ethyl-1-14C]N-nitrosoethylmethylamine (EMNA) 100 uM; and [2,5-14C]N-nitrosopyrrolidine (NPy) 100 uM. The metabolism of the carcinogens was assayed by the release of metabolites into the culture medium and the binding of radioactive metabolites to DNA. The human bladder cells retained 2 the capacity to metabolize chemical carcinogens. Binding of DNA occurred to a similar extent in all three cell lines. More BP was bound to DNA in human bladder cells than in rat bladder cells. More than 90% of the metabolites of BP in human cells consisted of organo-soluble products, primarily the 9,10-and 7,8-BP diols. N-nitrosamine metabolism produced CO2. NPy was oxidized in both the alpha and beta positions, predominantly alpha in human cells. EMNA was apparently metabolized, but did not bind to DNA. The results suggest that the human bladder may be able to activate carcinogens that come into direct contact with the epithelium, and that it utilizes pathways that are different from those found in other tissues and cells. (38 Refs)

INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS

9. COMPARATIVE CARCINOGENICITY OF TWO ISOMERS OF NITROSO-2,6-DIMETHYLMORPHOLINE IN GUINEA PIGS.

Lijinsky W, Reuber MD
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Lett; 14(1):7-11 1981

The carcinogenic effectiveness of the cis and trans isomers of nitroso-2,6-dimethylmorpholine (Me2NMOR) in male guinea pigs was compared. Twenty animals received cis Me2NMOR in oil by gavage at a concentration of 10.5 mg/ml at a dose of 0.2 ml 2x/wk for 30 wk. The other group of 20 animals received trans Me2NMOR in oil by gavage at a concentration of 5.3 mg/ml at a dose of 0.2 ml 2x/wk for 30 wk. A the end of 105 wk, the cis group had 2 surviving animals while the trans group had 7. There were 17 tumor-bearing animals in the cis group and 2 in the trans group. The major site of tumor induction in the cis group was the liver: 16 animals had liver tumors; hepatocellular carcinomas or cholangiocarcinomas; most animals had two tumor types, several had all three types. There were metastatic hemangiosarcomas in five animals, metastatic hepatocellular carcinoma in two, and metastatic cholangiocarcinoma in one. There were also significant numbers of tumors of the lung and adrenal cortex, and other types of tumor. None of these tumors were seen in the animals treated with the trans isomer nor in untreated guinea pigs of the same strain. The dis-

parate results with the two Me2NMOR isomers in rats as previously reported and in guinea pigs suggest that the mechanisms of activation in the two species might be different. (9 Refs)

10. CARCINOGENESIS IN SYRIAN HAMSTERS BY N-NITROSO-2,6-DIMETHYLMORPHOLINE, ITS CIS AND TRANS ISOMERS, AND THE EFFECT OF DEUTERIUM LABELING.

Rao MS, Scarpelli DG, Lijinsky W
Dept. Pathology, Northwestern Univ. Medical Sch., 303 East Chicago Ave., Chicago, IL, 60611
Carcinogenesis; 2(8):731-735 1981

Syrian golden hamsters were divided into groups of 20 each. They were given doses of N-nitroso-2,6-dimethylmorpholine (NDMM), its cis or trans isomer, or its alpha-d4 or beta-d2 deuterium-labeled derivatives. The weekly doses (mg/kg body wt) were NDMM 18 or 50; cis-NDMM 11.5 or 31; trans-NDMM 6.5 or 17; d4 18 or 50; d2 50. A total of 52 benign and 21 malignant tumors resulted, most associated with the pancreas, liver, respiratory system, and kidneys. The survival rate among hamsters treated with cis-NDMM was about the same as the rate for those treated with NDMM. The survival rate with trans-NDMM was higher, indicating that trans-NDMM was a less potent carcinogen. Treatment with d4 produced tumors earlier than treatment with d2, suggesting that d4 was the more potent of the two. The overall incidences of malignant tumors for the NDMM, d4, and d2 groups were not significantly different. Activation to mutagenicity by pancreas microsomes, and binding to DNA of the pancreas did not differ between the isomers. (21 Refs)

11. FLUORO-SUBSTITUTED N-NITROSAMINES. 1. INACTIVITY OF N-NITROSO-BIS-(2,2,2-TRIFLUOROETHYL)AMINE IN CARCINOGENICITY AND MUTAGENICITY TESTS.

Preussmann R, Habs M, Pool B, Stummeyer D, Lijinsky W, Reuber MD
German Cancer Res. Center, Inst. Toxicology and Chemotherapy, Heidelberg, W. Germany
Carcinogenesis; 2(8):753-756 1981

The LD50 of N-nitro-bis-(2,2,2-trifluoroethyl)amine (NBTFA) was determined to be 300 mg/kg in male Sprague Dawley rats. To test the carcinogenicity of NBTFA, rats were fed 3 mg NBTFA/kg body wt/day. They were observed for their lifetime or until killed when moribund. Fischer 344 female rats were fed 3.7 mg NBTFA, 1.8 mg diethylnitrosamine (DEN), or 0.7 mg DEN/kg/day. Treatment lasted 30 wk. Animals were allowed to die naturally. In both Sprague Dawley and Fischer rats, chronic treatment with NBTFA was found to have no carcinogenic effect. An equimolar amount of DEN produced 100% incidence of tumor s and was tumorigenic at much lower levels. Mutagenicity tests with Salmonella typhimurium strains TA1535 and TA100 with activation by rat hepatic S-9 fraction were negative. Apparently the presence of fluorine in the beta position of the DEN-derived NBTFA molecule blocks the alpha-oxidation thought to be necessary for the activation of carcinogenicity and mutagenicity of dialkylnitrosamines. (17 Refs)

12. PATHOLOGY OF METASTASIZING TUMORS IN NITROSOMETHYL UREA-INDUCED RAT MAMMARY CARCINOMA.

Ghosh L, Nassauer J, Faiferman I, Ghosh BC
(c/o B. C. Ghosh) Landow Building, Room 4804, NIH, NCI, 7910 Woodmont Ave., Bethesda, MD, 20205
J Surg Oncol; 18(1):21-26 1981

The metastatic capacity of rat mammary tumors induced with N-nitrosomethyl urea was tested in BUF/N inbred female rats by successive transplantation. After the first and second passage, tumor cells appeared diffusely distributed throughout the bone marrow and spleen, confirming results reported by others; no other metastases were observed. After six successive transplantations, large, well-defined tumor nodules were observed in the liver, spleen, lung, and the peritoneal surface of the intestines in 40% of the injected animals. The morphology of the primary and metastatic tumors was compared by light microscopy. The tumors appeared to be adenocarcinomas with differing degrees of differentiation. No morphological differences could be observed between the primary and the metastatic tumors. (Author abstract) (9 Refs)

13. DIFFERENTIATION OF THE MECHANISMS OF ONCOGENICITY OF 1,4-DIOXANE AND 1,3-HEXACHLOROBUTADIENE IN THE RAT.

Stott WT, Quast JF, Watanabe PG
Toxicology Res. Lab., Dow Chemical U.S.A., Midland, MI, 48640
Toxicol Appl Pharmacol; 60(2):287-300 1981

Two tumorigenic agents, 1,4-dioxane (DX) and 1,3-hexachlorobutadiene (HCBD) were compared to the known mutagen dimethylnitrosamine (DMN) to determine whether their actions were by a genetic or nongenetic mechanism. Male Sprague Dawley rats were given tumorigenic doses of DX in drinking water (0, 10 or 100 mg/kg/day for 11 wk), HCBD by gavage (0, 0.2, or 20 mg/kg/day for 3 wk), or DMN by gavage (3 mg/kg/day for 3 wk). Other groups of rats were given single doses of DX (10, 100, 1,000 mg/kg), HCBD (0.2, 20 mg/kg), or DMN (3 mg/kg) by gavage. DX produced no genotoxic effects at tumorigenic doses. A single large dose produced no alkylation of DNA or increase in DNA repair. Repeated high doses of DX were hepatotoxic. HCBD produced a minor genotoxic effect compared with DMN. DNA repair in renal tissue was increased 1.27-1.54-fold by HCBD (20 mg/kg); DNA alkylations occurred at the rate of 0.78 per 10(6) nucleotides. No mutations were produced in the Ames' bacterial mutagenesis assay. HCBD produced renal cytotoxicity. Apparently DX induces tumors by a nongenetic mechanism. HCBD acts primarily in a nongenetic way, but is weakly genotoxic. Risk from either compound is likely only at cytotoxic doses. (34 Refs)

14. FAILURE TO DISCRIMINATE INITIATION FROM PROMOTION OF LIVER TUMORS IN A LONG-TERM STUDY WITH THE PHENOBARBITAL-TYPE INDUCER ALPHA-HEXACHLOROCYCLOHEXANE AND THE ROLE OF SUSTAINED STIMULATION OF HEPATIC GROWTH AND MONOOXYGENASES.

Schulte-Hermann R, Parzefall W
Institut fur Toxikologie und Pharmakologie, Pilgrimstein 2, 335 Marburg, W. Germany
Cancer Res; 41(10):4140-4146 1981

The compound alpha-hexachlorocyclohexane (alpha-HCH) was administered po to female Wistar rats for periods of up to

33 mo; doses were 20 mg/kg/day, 200 mg/kg every 2nd wk, or 420 mg/kg every 3rd wk. Increases of liver size, DNA, RNA, and protein (by 50 to 100%) and of drug-metabolizing enzyme activities (up to 300%) observed previously after single doses of alpha-HCH were found to persist after approx 1/3, 1, and 2 yr of treatment. At 1 and 2 yr, DNA synthesis was measured by [3H]thymidine uptake and was no higher than in controls. All changes regressed upon withdrawal of alpha-HCH after 1 yr of treatment. These findings provide no evidence to suggest a protracted development of toxicity or of growth autonomy in the majority of liver cells. Foci of altered cells, neoplastic nodules, and in 2 animals hepatocellular carcinoma were detected histologically in the livers of 24 of 34 treated rats. In livers of 10 of 22 untreated control rats, foci of altered cells developed 'spontaneously' between 12 and 34.5 mo. If neoplastic lesions were induced by a single dose of diethylnitrosamine, 75 or 150 mg/kg, subsequent treatment with alpha-HCH led to the appearance of hepatocellular carcinoma within 7 mo. Altogether, hepatocellular carcinomas were found in 18 of 21 rats treated with both agents but in only 3 of 26 animals treated with diethylnitrosamine alone. The results show that determination of tumor numbers alone in a long-term animal experiment does not allow one to decide whether alpha-HCH (and similar 'xenobiotic inducers') is an initiating carcinogen or merely promotes tumorigenesis from 'spontaneous' lesions. Our findings support the latter possibility by the failure to detect evidence suggesting initiating potential of alpha-HCH, by the enhanced mitotic response to alpha-HCH in foci of altered cells as reported elsewhere, and by the observation of a permanent stimulatory action on liver growth during prolonged exposure to alpha-HCH. (Author abstract) (46 Refs)

15. ENZYME DEVIATION PATTERNS IN PRIMARY RAT HEPATOMAS INDUCED BY SEQUENTIAL ADMINISTRATION OF TWO CHEMICALLY DIFFERENT CARCINOGENS.

Sato K, Hatayama I, Hoshino K, Imai F, Tsuchida S, Sato T, Nishimura K, Tatematsu M, Ito N
Second Dept. Biochemistry, Hirosaki Univ. Sch. Medicine, Hirosaki 036, Japan
Cancer Res; 41(10):4147-4153 1981

Enzyme deviation patterns were examined in primary rat hepatomas induced by short-term sequential administration of two chemical carcinogens from among 2-fluorenylacetamide (FAA), diethylnitrosamine (DENA), and 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) or by FAA or 3'-Me-DAB followed by phenobarbital as a promoter. The purpose was to discern how the patterns are influenced by different administration schedules of carcinogens and which of the two carcinogens in the sequence affects the patterns more. Biochemical differentiation of hyperplastic hepatic nodules and hepatomas was determined by simultaneous assays of activities and isozyme composition of glucose-adenosine triphosphate phosphotransferase, pyruvate kinase, glucose-6-phosphatase, fructose-1,6-biphosphatase, and gamma-glutamyltransferase with consideratio of histological classification of nodules and tumors. Poorly differentiated hepatomas were predominantly induced by 3'-Me-DAB followed by FAA or DENA except for hepatomas induced by 3'-Me-DAB followed by phenobarbital, which were mainly well and moderately differentiated; well and moderately differentiated hepatomas were predominantly induced by FAA followed by 3'-Me-DAB or phenobarbital. The degree of enzyme deviation of the hepatomas induced by DENA as the first carcinogen was intermediate between those of hepatomas induced by FAA or 3'-Me-DAB, although the degree tended to increase with increased dose or term of DENA. These results indicate that deviations of some enzymes, such as pyruvate kinase and fructose-1,6-bisphosphatase, as well as histological differentiation of the primary hepatomas are more strongly influenced by the first carcinogen than by the second under our administration schedules and that the degree of enzyme deviation shown by hepatomas produced by a particular carcinogen treatment regimen principally relates to the potential of that regimen to induce the more anaplastic tumors. (Author abstract) (33 Refs)

16. EARLY EVENTS DURING LIVER CARCINOGENESIS INVOLVING TWO CARCINOGEN:PROTEIN COMPLEXES.

Blackburn GR, Andrews JP, Custer RP, Sorof S
(c/o Sorof), Inst. Cancer Res., Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA, 19111
Cancer Res; 41(10):4039-4049 1981

This report describes the relationships between the levels of two principal carcinogen:protein complexes and histological alterations that occur during carcinogenesis in rat liver by three carcinogens. An intragastric tracer dose of N-[9-14C]-2-fluorenylacetamide interacts in normal rat liver to form the principal cytosolic 14C-carcinogen:protein complex (2S; M.W. 14,700). Continued ingestion of any of three hepatocarcinogens causes the marked loss of the 2S complex and the concurrent gain of a large-mol-wt carcinogen:protein complex (7.5S; M.W. approx 150,000) 48 hr following a dose of N-[9-14C]-2-fluorenylaceta mide. The reciprocal changes in amounts of the two complexes have the following properties. The alterations occur early during hepatocarcinogenesis. In contrast to other reported early events, chemical carcinogen is directly involved. The two labeled fluorenyl proteins are the principal 14C-carcinogen:protein complexes in rat liver cytosol. Formation of the two complexes apparently involves activation of the carcinogen N-2-fluorenylacetamide. The reciprocal effects are brought on by the ingestion of any of the three hepatocarcinogens, N-2-fluorenylacetamide, 3'-methyl-4-dimethylaminoazobenzene, and ethionine. The loss of the 2S complex was previously demonstrated to be associated with the loss of the 2S protein itself (14,700-daltons polypeptide) to which the carcinogen is bound. The rate of inversion in concentrations of the two complexes is apparently related to the susceptibility of the strain and sex of rat to the carcinogen; the greater the susceptibility the more rapid is the rate. The time of the max inversion coincides approx with the appearance of putative malignant lesions. Cessation of N-2-fluorenylacetamide ingestion results in the symmetrical reversal of the reciprocal changes in the levels of the two complexes. Liver regeneration following partial hepatectomy brings about a moderate inversion of the levels of the two complexes, suggestive of the possibility that the cell proliferation associated with hepatocarcinogenesis may be casually related to the effects. Consistent with this possibility, the 2S protein has a mol wt like those of known polypeptide growth regulators. The effects on the 2S and 7.5S carcinogen:protein complexes are carcinogen group specific, inasmuch as the ingestion of any of three other types of liver carcinogens, namely, diethylnitrosamine,aflatoxin B, and thioacetamide, does not induce the reciprocal changes in the levels of the two complexes. The existence of such carcinogen group specificity suggests that chemical classes of carcinogens may be grouped on the basis of their common actions and effects on their target macromolecules. The generalizations to be derived from a classification of carcinogen group specificities seem likely to advance understanding of underlying events in chemical oncogenesis. (33 Refs)

17. CANINE GASTRIC CARCINOMA AS AN ANIMAL MODEL OF HUMAN GASTRIC CARCINOMA.

Matsukura N, Morino K, Ohgaki H, Kawachi T
Div. Biochemistry, Natl. Cancer Center Res. Inst., Tokyo 104, Japan
I To Cho; 16(7):715-722 1981

Conditions needed to induce gastric cancer in dogs which resembles that found in humans were investigated, and the advantages of canine experimental gastric cancers as models were discussed with respect to human gastric cancer. Gastric carcinoma was induced in 15/15 male beagles that were given N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG; 100 or 150 ug/ml drinking water) for 5-9 mo. The eight dogs given 100 ug/ml of the ENNG primarily developed depressed-type early gastric carcinoma and Borrmann Type 2 or 3 advanced gastric carcinomas of the gastric angle and antrum. The seven dogs given 150 ug/ml of the ENNG primarily developed protruded or depressed-type early gastric carcinoma, Borrmann Type 1-like carcinomas and Type 3 advanced gastric carcinomas of the gastric angle, antrum, and a few on the corpus. Labeling indices (LIs) of canine gastric carcinoma were examined in vivo with pulse injection of methyl-3H thymidine iv. The LIs of cancerous lesions were lower than those of noncancerous gastric mucosa or that of untreated dogs. The LIs differed according to histological types of tumors and to the area of the particular lesion. Canine gastric cancers were thought to be valuable models for basic research on carcinogenesis and chemotherapeutic regimens. (10 Refs) (In JPN)

18. CLINICAL APPLICATION OF AN EXPERIMENTAL GASTRIC CANCER MODEL AND ITS CONTRIBUTION.

Saito T, Sasaki O, Matsuguchi T, Iwamatsu M, Sano C, Inokuchi K
First Dept. Surgery, Oita Medical Coll., Oita, Japan
I To Cho; 16(7):727-736 1981

Results of examining experimental gastric cancers induced in rats, hamsters, rabbits, mice, and dogs were analyzed with respect to clarifying indicators of precancerous conditions, influence of ulcerations on cancer growth, relationships between peripheral lesions and DNA histograms, and stages of cancerous growth. Observation of the process of carcinogenesis in animals with induced cancers showed that erosion, mucosal atrophy, ulcers, ulcer scars, and hyperplastic polyps occurred prior to the manifestation of a cancer; this suggested that these lesions should be followed clinically as precancerous. Formalin-induced chronic ulcers were observed to enhance the induction of cancer with N-methyl-N'-nitro-N-nitrosoguanidine in rats. From histological studies of microcancers that occurred in experimental canine gastric cancers, it was thought that well-differentiated carcinoma developed in severely eroded mucosa and poorly-differentiated carcinoma developed in mildly or non-eroded mucosa. Three types of experimental canine gastric cancer were proposed on the basis of their mode of growth; one type was elevated and two were depressed. (55 Refs) (In JPN)

19. CONTRIBUTION OF THE STUDY OF EXPERIMENTAL CANINE GASTRIC CARCINOMA TO THE STUDY OF HUMAN GASTRIC CARCINOMA.

Kurihara M, Izumi T, Shirakabe H, Okui K, Miyazaka K, Maruyama S, Sasaki Y, Inaguma H, Kamano Y, Yasui A, Suwa B
Third Dept. Internal Medicine, Saitama Medical Sch., Saitama 350-04, Japan
I To Cho; 16(7):737-744 1981

Induction of experimental gastric carcinoma in dogs by N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) soln was investigated, and the dynamics of 5-fluorouracil (5FU) and uracil + 5-fluoro-1-(tetrahydro-2-furyl)-uracil (UFT) were studied in dogs bearing cancers. Gastric carcinomas were induced easily in the dogs by administering ENNG po 2x/day (13.8-23.8 g total) with food pellets, but scirrhous type gastric carcinoma was rarely induced with ENNG alone. On the other hand, 3/10 beagles given ENNG and gastrin developed scirrhous type carcinoma; all three tumors were observed in the pyloric and antrum regions of the stomach and were poorly differentiated adenocarcinomas. Signet ring cell carcinoma in the submucosa and marked proliferation of collagen fibers in the antrum were also observed. After iv injection and po administration of 14C-5FU to the ENNG-induced tumor-bearing dogs, higher concentrations of 5FU were observed in the cancer tissues (both superficial and deep) than in the normal tissues. Similar tests of UFT in a dog with ENNG-induced gastric carcinoma showed that 5FU concentrations were higher in the stomach and lungs than other tissues. (25 Refs) (In JPN)

20. EXPERIMENTAL CANINE GASTRIC CARCINOMA AS A MODEL TO STUDY EFFECTS OF ANTICANCER DRUGS.

Tanaka Y, Uosumi G, Inokuchi H, Aoike A, Kawai K
Dept. Preventive Medicine, Kyoto Prefectural Univ. Medicine, Kyoto 602, Japan
I To Cho; 16(7):745-750 1981

Experimental gastric carcinomas were induced in eight beagle dogs by means of N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG), and the effects of a schizophyllum polyglucan (SPG) on the cancers were studied. Ten dogs were divided into four groups: Groups I (3 dogs), II (3), and III (2) were administered the ENNG, and Group IV (2) was not; Groups I and II were given SPG (2 mg/kg/wk) + Freund's incomplete adjuvant (FIA), while Group III was given NaCl + FIA and Group IV was given NaCl alone. The SPG was administered sc in all groups. Group I dogs were given the SPG 12 mo after administration of the ENNG and after cancerous lesions were observed. Group II dogs were given the SPG 5 mo after administration of the ENNG and while no cancerous lesions were observed. Changes in mitogen responses of peripheral lymphocytes from the dogs to concanavalin A and phytohemagglutinin were not observed in the dogs administered SPG, but the dogs not administered the SPG showed decreased mitogen response. However, as endoscopic examination of the cancers in the dogs given the SPG showed advancing growth of the tumors, therapeutic effect was doubted. The canine gastric cancer model was thought to be applicable for immunotherapy studies of human gastric cancers. (12 Refs) (In JPN)

21. MORPHOGENESIS OF EXPERIMENTAL CANINE GASTRIC CARCINOMA, PARTICULARLY THE DEVELOPMENT OF THE 'DOUBLE-LAYER STRUCTURE' OF SIGNET RING CELL CARCINOMA.

Sunagawa M, Murakami T, Takeshita K, Nakajima A, Hoshi K, Menjo M
First Dept. Surgery, Tokyo Medical and Dental Univ. Sch. Medicine, Tokyo, Japan
I To Cho; 16(7):751-756 1981

An N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG)-induced gastric carcinoma that was produced in a female beagle was examined with 5 mm-width serial sectioning and staining. The cancer nest, 3-5 mm in diameter, was observed 11 mo after the initial 6-mo ENNG treatment period (11.7 g ENNG total). Borrmann 3 type cancer (poorly differentiated adenocarcino-

ma), Type I early stage cancer (well-differentiated tubular adenocarcinoma), and Type IIc early stage cancer (signet-ring cell carcinoma and poorly differentiated adenocarcinoma) were observed in the resected stomach as well as numerous microcarcinomas (signet-ring cell carcinomas and highly-differentiated tubular adenocarcinomas) in the mucosa. Examination of 5 um thick sections with various stains showed double-layer structures indicating that signet-ring cells infiltrated the mucosa propria in the area where the basement membrane was disrupted. Results indicated that signet-ring cell carcinoma might have developed from a double-layer structure in the gastric gland itself. These findings were confirmed by examination of the stomach from a dog given ENNG for only 3 mo; the stomach showed multiple minute foci consisting only of signet-ring cells with a double-layer structure. (9 Refs) (In JPN)

22. EXPERIMENTAL CANINE GASTRIC CARCINOMA WITH METASTASES TO THE LIVER, SPLEEN, LUNGS, AND LYMPH NODES.

Uozumi G, Tanaka Y, Fujimoto S, Tsuchihashi Y, Sugimoto H, Kawai K

Dept. Preventative Medicine, Kyoto Prefectural Univ. Medicine, Kyoto 602, Japan

I To Cho; 16(7):757-760 1981

Lung, spleen, liver, and lymph node metastases were observed in a 16-mo-old male beagle with an N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG)-induced Borrmann Type 3 adenocarcinoma of the region of the antrum and gastric angle. The dog was given 500 ml of 150 ug ENNG/ml water/day for 8 mo. The metastatic nests were adenocarcinomas that were histologically consistent with the primary gastric tumor. Metastasis has rarely been observed in dogs administered ENNG. (9 Refs) (In JPN)

23. PRODUCTION OF BORRMANN TYPE 3 GASTRIC CANCER IN DOGS TREATED WITH LOW CONCENTRATIONS OF ENNG.

Fujita M, Nampei S, Tsukahara Y, Taguchi T, Sato M

Dept. Surgery, Res. Inst. for Microbial Diseases, Osaka Univ., Osaka, Japan

I To Cho; 16(7):761-767 1981

Endoscopic, radiographic, and histologic examinations of gastric cancers induced in 8/15 dogs by means of low concentrations of N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG; 50 ug/ml/day; 3.4-9.2 g total) administered for 30-52 wk were performed. Of the eight dogs that had gastric carcinoma, seven died of advanced gastric cancer up to 5 yr after initiation of the experiment. The primary tumor nests were Stage I in one case, II in one, III in one, and IV in four. Six of the dogs developed Borrmann Type 3 cancer fro m poorly-differentiated adenocarcinoma; serial examination of these tumors indicated that the primary tumor nests developed from Type IIc early stage carcinoma. Examination of the Borrmann Type 3 lesions showed limited cancerous spread in the mucosal layer, signet-ring cell cancer limited to small areas around the ulcer, diffuse infiltration of the submucosal layer, and invasion of poorly-differentiated adenocarcinoma to the serosa. Results indicated that this animal model can be used to study human gastric carcinoma. (16 Refs) (In JPN)

24. A NEW PROSTATIC CANCER MODEL: SYSTEMIC INDUCTION OF PROSTATIC CANCER IN RATS BY A NITROSAMINE.

Pour PM

Toxicology Dept., Sandoz AG, Preclinical Res., CH-4133 Prattein 4, Switzerland

Cancer Lett; 13(4):303-308 1981

Fifteen 8-wk-old male Wistar-derived MRC rats received 10 mg/kg body wt N-nitrosobis(2-oxopropyl) amine (BOP) dissolved in physiologic saline by intragastric intubation each wk for life. Five of the treated rats (33%) but no controls developed prostatic cancer approx 50 wk after treatment had begun. Four (10-20 mm) tumors were macroscopically visible as greyish white lobulated nodules invading the surrounding tissue. Histologically all carcinomas were of the keratinizing cell type with areas of anaplasia. No adenomatous components were seen. Hyperplasia and metaplasia of the prostatic gland were found in 13 rats with or without cancer. Most tumors appeared to have originated in the suburethral dorsal prostate. Prostatic cancer was associated with simultaneous squamous cell papilloma or carcinoma of the urethra, with av incidence 67%. Tumors induced in other tissues included neoplasms of the nasal cavities (47%), lung (40%), colorectum (47%), liver (47%), kidneys (13%), and thyroid (27%). Disadvantages of the model are the simultaneous induction of neoplasms in nonprostatic tissue and the squamous cell character of the prostatic cancer. Also contrary to the human form is the absence of distant metastases. Mechanisms of tumor development are discussed. (18 Refs)

25. LUNG ENDOCRINE-LIKE CELLS IN HAMSTERS TREATED WITH DIETHYLNITROSAMINE: ALTERATIONS IN VIVO AND IN CELL CULTURE.

Linnoila RI, Nettesheim P, DiAugustine RP

Lab. pathology, NCI, NIH, Bethesda, MD, 20205

Proc Natl Acad Sci USA; 78(8):5170-5174 1981

Diethylnitrosamine is known to cause squamous cell carcinoma and adenocarcinoma of the lung in Syrian golden hamsters. Sections of lungs obtained from hamsters treated with the systemic carcinogen diethylnitrosamine showed a significant increase in the number of argyrophilic cells of neuroepithelial bodies. The hyperplastic response was retained at least 4 wk after cessation of treatment. To examine whether these affected cells exhibited enhanced survival in vitro, lung cells were dissociated with Pronase a nd grown in culture. After 7 days, argyrophilia, dense-cored vesicles, and corticotropin-like immunoreactivity were observed in many of the cells derived from hamsters treated for 5 or 8 wk. These findings suggest that the endocrine-like cells of neuroepithelial bodies are affected by diethylnitrosamine as evidenced by a numerical increase in vivo and by the properties exhibited by cells in vitro. The relationship of this diethylnitrosamine-induced reaction to bronchial carcinoid tumors or small-cell carcinoma of the lung remains to be established. (Author abstract) (46 Refs)

26. THE DEVELOPMENT OF BRAIN TUMOURS PRODUCED IN RATS BY THE INTRACEREBRAL INJECTION OF NEOPLASTIC GLIAL CELLS: A FINE STRUCTURAL STUDY.

Davaki P, Lantos PL

(c/o Lantos) Dept. Neuropathology, Inst. Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, England

Neuropathol Appl Neurobiol; 7(1):49-61 1981

Tumors were produced in all 126 BD-IX rats given intracerebral injection of 5 x 10(5) cells from a glial cell clone derived from N-ethyl-N-nitrosourea-induced BD-IX rat glioma. Cells were suspended in 25 ul buffer; 26 control rats received similar injections of buffer. Groups of rats were killed 1, 3, and 5 days and 1, 2, 3, and 4 wk after injection; the brains were fixed b in vivo perfusion. Both light and electron microscopic findings are reported. Tumors diffusely invaded the surrounding areas without formation of capsules. All were malignant astrocytomas, and their malignancy increased with time after injection. At 1 and 2 wk they were chiefly fibrillary astrocytes; at 3 and 4 wk they contained a higher proportion of undifferentiated cells and intermediate cell types, indicating increasing anaplasia. Thus, glial character of the tumor was maintained throughout although features changed with time. This tumor, with its short latent period, may be used as a reproducible brain tumor model in chemo- and radiotherapy and other studies. (21 Refs)

MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS

27. INFLUENCE OF ETHYL ALCOHOL ON CARCINOGENESIS WITH N-NITROSODIMETHYLAMINE.

Griciute L, Castegnaro M, Bereziat JC

Inst. Epidemiology, Microbiology, and Hygiene, 64 Gorki St., Vilnius 232024, Lithuania, USSR

Cancer Lett; 13(4):345-352 1981

The carcinogenic action of N-nitrosodimethylamine (NDMA; 0.03 mg by gavage x 2/wk) administered for 50 wk in either water or 40% ethanol was examined in 208 C57BL 8-wk-old mice. The mice were divided into the following treatment groups: (1) NDMA in ethanol, (2) NDMA in water, and (3) ethanol only. Death from tumors in groups 1 and 2 began, respectively, at wk 30 and 38; all group 3 subjects survived beyond 50 wk. Most notably, frontal brain lobe malignant tumors appeared only in group 1. Greyish infiltrating masses arising from the posterior nasal fossa were detected in 12/36 males and 12/30 females. Tumors were microsco pically identical; histological appearance was typical of olfactory neuroepithelioma. No metastases were found. Groups 1 and 2 exhibited other malignant and benign liver tumors and lymphomas. Lymphomas and benign tumors were also found in group 3. Tumor rate (21%) was significantly lower in group 3 than in groups 1 (48%) and 2 (43%); morbidity for malignant liver tumors was significantly lower in group 1 (16%) than in group 2 (30%). Alcohol by itself was not carcinogenic but was associate a change in target for the liver carcinogen NDMA: development of infiltrating olfactory neuroepithelioma was favored. (14 Refs)

28. EFFECTS OF CHLOROFORM AND DIMETHYLNITROSAMINE ON RENAL CARCINOGENESIS IN UNILATERALLY NEPHRECTOMIZED RATS FED FORMIC ACID 2-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL]HYDRAZIDE.

Hirose M, Imaida K, Ito H, Hayashi M, Ishihara Y, Ito N

First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan

Carcinogenesis; 2(8):703-708 1981

Male Fischer rats were divided into five groups. Group 1 was subjected to unilateral nephrectomy (UN). After 2 days dimethylnitrosamine (DMN: 20 mg/kg body wt) was injected ip. One wk after UN the rats were placed on a diet containing O.2% 2-[4-(5-nitro-2-furyl)thiazolyl]hydrazide (FNT). Two wk after UN they received CHCl3 (400 mg/kg body wt). Group 2 received the same treatment without the FNT diet. Group 3 received the same treatment as group 1, except that CHCl3 treatment came before UN. Group 4 received the same treatment as group 3, but without FNT. Group 5 received only the FNT diet. Rats from each group were studied at 8, 16, and 32 wk. Renal tubular hypertrophy was found in 100% of groups 1, 3, and 5 at all three times. Tubular hyperplasia was found in group 1 (0%, 53.3%, 100%), group 3 (20%, 52.9%, 94.4%) and group 5 (0%, 0%, 94.1%) at 8, 16, and 32 wk, respectively. Renal cell tumors were found at 32 wk in groups 1 (85%), 3 (88.9%), and 5 (17.6%). No tumors were found in groups 2 and 4. The results from groups 2 and 4 show little or no initiating effect for FNT. Slight enhancement of renal tumors was produced by UN. The results from groups 1 and 3 indicate that UN and CHCl3 treatments had about equal effect in inducing preneoplastic changes in rat kidney. The enhancement of tubular hyperplasia and renal cell tumors by combined treatment with CHCl3, DMN, UN, and FNT in the initiating and promoting stages was confirmed. (22 Refs)

29. EFFECT OF PRETREATMENT WITH PREGNENOLONE-16ALPHA-CARBONITRILE AND PROTEIN-FREE DIET ON THE METABOLISM AND CARCINOGENICITY OF DIMETHYLNITROSAMINE.

Kiessling M, Lipinski R, Bohm N, Kleihues P

Pathologisches Institut, Universitat Freiburg, 78 Freiburg, W. Germany

Carcinogenesis; 2(8):757-761 1981

Adult female Wistar rats were pretreated with a protein-free diet (PFD), pregnen olone-16alpha-carbonitrile (PCN: total dose 25 mg, 5 equal doses at 12-hr intervals), or a combination of both. Rats from each group were given a single injection of 60 mg dimethylnitrosamine (DMN). PCN-pretreated rats showed a 50% tumor incidence after a mean survival time of 672 days. PFD (30 rats) and PFD + PCN (28 rats) groups showed a tumor incidence of 83-85% and a mean survival time of 357 and 396 days. Rats treated only with PCN showed a tumor incidence of 50% with a mean survival time of 805 days. The incidence of neoplasms, particularly cholangiomas, was highest following treatment with PCN only. The PFD and PFD + PCN groups showed lower incidence of cystic cholangiomas and no malignant liver tumors. Methylation of liver DNA purines by a single dose of [14C] DMN was greatest in the PCN and PFD groups and lower in the PFD + PCN group. Methylation of renal DNA was highest in the PFD and PFD + PCN groups and lower in the PCN-only pretreated group. Differences in lung tissue were smaller among the various groups. Both PCN and PFD reduced the hepatotoxicity of DMN. PCN had no effect on the induction of renal tumors. Apparently PCN does not cause a reduction in DNM metabo-

lism in the liver and the resultant increase in DNA methylation in the kidney. PFD shifts the metabolism of DMN from the liver to the kidney, lowering the carcinogenic effect of DMN in the liver and raising it in the kidney. (24 Refs)

30. INFLUENCE OF THE ESTROUS CYCLE DURING CARCINOGEN EXPOSURE ON NITROSOMETHYLUREA-INDUCED RAT MAMMARY CARCINOMA.

Lindsey WF, Das Gupta TK, Beattie CW
(c/o Beattie) Div. Surgical Oncology, Univ. Illinois Medical Center, 840 South Wood St., Chicago, IL, 60612
Cancer Res; 41(10):3857-3862 1981

The influence of individual stages of the rat estrous cycle during exposure to l-nitroso-l-methylurea (NMU) on mammary tumor incidence, latency, number, and cytosol receptor dynamics for estrogen and progesterone was determined. Virgin female Buffalo rats were separated into three groups on day 53 according to their vaginal smear pattern. NMU (5 mg/100 g body wt, iv) was administered in 3 mo doses beginning at 53 to 55 days of age on diestrus, proestrus, or estrus between 9:00 and 11:00 a.m. Groups of rats had their second and third injections of NMU on the same day of the estrous cycle as their initial injection. All animals were killed during the morning on a diestrus day. Receptors for estrogen and progesterone were determined by a modified dextran-coated charcoal method and by sucrose density gradient analysis. Mean latencies to first tumor appearance in diestrus, proestrus, and estrus groups were 104.4, 83.6, and 91.4 days, respectively (p less than 0.05, diestrus versus estrus and proestrus) following the NMU injection. The mean number of tumors per rat was significantly higher in rats injected on proestrus (4.5) or estrus (4.3) than on diestrus (2.0). Estradiol bound to receptor sedimented at 8 and 4 s and was suppressed by diethylstilbestrol and estradiol. Progesterone receptor migrated to 7.8 and 4 s regions. Estrogen receptor incidence (100%) and content (16.7 fmol/mg cytosol protein) was highest in rats injected on diestrus. In the proestrus and estrus injected groups, estrogen receptor incidence was 95 and 63% and content was 10.2 and 11.2 fmol/mg protein, respectively. The affinity of estradiol for its receptor was not significantly altered in any group. Although there were no statistically significant differences in progesterone receptor incidence or affinity between groups, progesterone receptor content (74.6 fmol/mg cytosol protein) was significantly higher in tumors from rats injected on proestrus than on diestrus. These data suggest that the prevailing hormonal milieu of the estrous cycle during NMU exposure may be critically important to the subsequent biological behavior and steroid receptor status of carcinogen-induced rat mammary tumors. (Author abstract) (41 Refs)

31. SEX DIFFERENCES IN THE EFFECTS OF RETINOIDS ON CARCINOGENESIS BY N-NITROSOBIS(2-OXOPROPYL)AMINE IN SYRIAN HAMSTERS.

Birt DF, Sayed S, Davies MH, Pour P
Eppley Inst. for Res. in Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105
Cancer Lett; 14(1):13-21 1981

Male and female Syrian hamsters received a single dose of N-nitrosobis(2-oxopropyl)amine (BOP: 40 mg/kg, sc) and 1 wk later were fed one of four retinoid types (13-cis-retinoic acid (13-cis-RA), N-ethylretinamide (ERA), 2-hydroxy-ethylretinamide (OH-ERA), or 4-hydroxyphenylretinamide (PRA)) each at three dose levels reported as 0.05, 0.1, and 0.2 milliM/kg diet. The wt of the pancreas was influenced by the sex and retinoid level: wt increased in females fed the high retinoid level and decreased in males fed the 0.1 milliM level. Nearly all animals developed pancreatic adenomas. The av number of adenomas was reduced in female hamsters fed retinoids. The greatest decrease occurred with 13-cis-RA (48% reduction), with reductions intermediate for ERA and OH-ERA (39%), and smallest for PRA (14%). In male hamsters, pancreatic adenoma incidence was not influenced by retinoid treatment; however, the multiplicity of these lesions in males fed OH-ERA and PRA was greater than those fed 13-cis-RA, ERA, or control diet. The pancreatic carcinoma incidence was not influenced by retinoids, although female hamsters fed 13-cis-RA developed fewer carcinomas per animal than did animals fed ERA. In female, but not male, hamsters, the liver tumor incidence was reduced from 60% to 21% by feeding OH-ERA, and the gallbladder tumor incidence from 60% to less than 10% in females fed 13-cis-ERA and ERA. These results suggest that sex hormones or other sex differences may influence t he factors which determine the ability of retinoids to inhibit carcinogenesis. (33 Refs)

32. ASCORBIC ACID AND CANCER OF THE DUODENUM. AN EXPERIMENTAL STUDY.

Werner B, Denzer U, Mitschke H, Brassow F
Abteilung fur Allgemeinchirurgie, Universitat, Martinistrasse 52, D-2000 Hamburg 20, W. Germany
Langenbecks Arch Chir; 354(2):101-109 1981

The effect of vitamin C (administered po as sodium ascorbate, 2-3% in feed) on carcinoma of the small intestine induced by N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG: 120 mg/liter in drinking water) was studied in male Wistar rats. Group I was treated with ENNG only, Group II with ENNG and vitamin C simultaneously, and Group III with vitamin C only. The duration of each experiment was 18 wk. The number of tumor-bearing animals was 33/36 in Group I, 32/35 in Group II, and 0/10 in Group III. The total number of tumors was 156 in Group I and 136 in Group II. Gastric tumors were found in one animal in Group I and in three in Group II. The number of suprapapillary duodenal tumors was 88 in Group I and 96 in Group II, that of intrapapillary duodenal tumors 62 in Group I and 37 in Group II. Five jejunal tumors were found in Group I. Adenoma and borderline lesions were found in 4/36 animals in Group I and in 8/35 in Group II. The depth of carcinoma infiltration corresponded to Stage P2 in 1/36 animals in Group I and in 8/35 in Group II, to Stage P3 in 3/36 and 3/35 animals in Groups I and I respectively, and to P4 in 25/36 animals in Group I and in 13/35 animals in Group II. The findings indicate that vitamin C did not suppress tumor induction, but caused a change in the distribution of the small intestinal tumors according to localization, and a significant reduction (p less than 0.005) in the frequency of Stage P4. (20 Refs) (In GER)

MUTAGENICITY OF NITROSO COMPOUNDS

33. MUTAGENICITY OF REACTION PRODUCTS OF SULPYRINE WITH NITRITE.

Sakai A, Yoshikawa K, Tanimura A, Tomita I
Div. Food Additives, Natl. Inst. Hygienic Sciences, Kamiyoga 1-18-1, Setagaya-ku, Tokyo, Japan
Mutat Res; 90(1):57-65 1981

The mutagenicity of three N-nitroso products of sulpyrine (1-diketobutyryl-1-phenyl-2-methyl-2-nitrosohydrazide hydrate

(DPMN), 4-(N-methyl-N-nitroso)aminoantipyrine (MNAA), and 1-acetyl-1-methyl-2-nitroso-2-phenylhydrazine) and of related compounds (4-methylaminoantipyrine, 1-acetyl-1-methyl-2-phenylhydrazine, 4-hydroxyantipyrine, sulpyrine, and sodium nitrite) was tested on Salmonella typhimurium TA100 and TA98. DPMN, MNAA, and sodium nitrite were mutagenic to TA100 but not to TA98. None of the other compounds were mutagenic to either strain. Activation of mutagenicity with rat-liver microsomal preparation (S9 mix) was required by MNAA, but not by DPMN. The addition of L-cysteine or glutathione markedly increased the mutagenicity of DPMN; the enhancing effects w ere proportional to concentration added. The possibility that sulpyrine might pose a carcinogenic hazard in man is discussed. (25 Refs)

34. MUTAGENICITY OF AMIDE TYPE AND CARBAMATE TYPE DIAZOALKANE-GENERATING AGENTS IN SALMONELLA/MICROSOME ASSAY.

Morita T, Sawaki M, Mifuchi I
Shizuoka Coll. Pharmacy, 2-2-1 Oshika, Shizuoka, 422, Japan
Chem Pharm Bull (Tokyo); 29(6):1758-1762 1981

Both amide type and carbamate type N-nitroso compounds, which have a common structure and have been reported to be excellent diazoalkane-generating compounds were examined for mutagenicity by measuring their ability to create histidine (his) prototrophic revertants of two his-dependent Salmonella typhimurium strains: T100 (a base-pair substitution strain) and TA98 (a frameshift strain), with and without metabolic activation by S-9 mix. Six compounds of each type having systematic substitutions at two different sites of the basic common structure were examined systematically over dose ranges of 0.27-2.7 umole (4 x 10(-5) to 4 x 10(-2) M). In the absence of activation, none of the amide type compounds showed any mutagenicity in either strain. With metabolic activation, two of six amide type compounds (both having a benzyl group in the same position) were weakly mutagenic to TA100. In the absence of S-9 mix, only one of six carbamate type compounds showed any mutagenicity (against TA98); in the presence of S-9 mix, all six carbamate compounds were mutagenic against TA100 over a wide range of concentrations and two of six were weakly mutagenic against TA98. There is apparently a structure-mutagenicity relationship for amide type and carbamate type compounds that is principally dependent upon the rate of chemical generation of diazoalkane or phenyldiazomethane in alkaline soln. (8 Refs)

35. INDUCTION OF SISTER CHROMATID EXCHANGES AND CHROMOSOME ABERRATIONS IN CULTURED MAMMALIAN CELLS BY N-NITROSOCIMETIDINE.

Athanasiou K, Kyrtopoulos SA
(c/o Kyrtopoulos) Natl. Hellenic Res. Foundation, Biological Res. Centre, 48 Vassileos Constantinou Ave., Athens 701, Greece
Cancer Lett; 14(1):71-75 1981

The possibility that N-nitrosocimetidine (NC), formed by the nitrosation of cimetidine (used in the treatment of gastric disorders), induces sister chromatid exchanges (SCE) and chromosomal aberrations in cultured Chinese hamster ovary cells (CHO) was investigated. NC caused a concentration-related increase in both SCE and chromosome aberrations in a concentration as low as 1.2 x 10(-7) M. At a concentration of 1.2 x 10(-4) M the number of SCE was too great to allow accurate counting and chromosome aberrations were induced in more than 90% of the metaphases. The chromosome aberrations observed were all of the chromatid type. On a molar basis, NC was approx two-thirds as potent an inducer of SCE as the gastric carci nogen N-methyl-N'-nitro-N-nitrosoguanidine. These findings constitute further evidence that NC possesses carcinogenic activity. (10 Refs)

36. INDUCTION OF 6-THIOGUANINE RESISTANCE IN SYNCHRONIZED HUMAN FIBROBLAST CELLS TREATED WITH METHYL METHANESULFONATE, N-ACETOXY-2-ACETYLAMINOFLUORENE AND N-METHYL-N'-NITRO-N-NITROSOGUANIDINE.

Huang SL, Huang SM, Casperson C, Waters MD
Northrop Services, Inc., Research Triangle Park, NC, 27709
Mutat Res; 83(2):251-260 1981

The conditions required for inducing mutations in cultured, synchronized human fibroblasts were studied by examining induction of 6-thioguanine (6TG) resistance in these cells following treatment with methyl methanesulfonate (MMS; 6.25-25 ug/ml), N-acetoxy-2-acetylaminofluorene (NA-AAF; 7.5-17.5 uM), or N-methyl-N'nitro-N-nitrosoguanidine (MNNG; 5-80 uM) at different times during the G1, S, and G2 phases of the cell cycle. NA-AAF mutagenesis was dose-dependent when it occurred; NA-AAF induced no mutations during G1; but it induced an increasing frequency of mutations during S phase, with the highest frequency occurring simultaneously with the peak in DNA synthesis and the frequency declining thereafter. MMS induced mutations in treatment that included G1 and S phases and S and G2 phases, but not in the treatment that included G2 and G1 phases, indicating that mutagenesis requires DNA synthesis. Induction of mutation by MNNG followed one-hit kinetics, but mutations resulting from NA-AAF followed a higher-order function. All three chemicals resulted in an increase both in the mutation frequency and in the absolute number of mutants. Mutation in the cells studied appears to require the use of S-phase cells, regardless of the mutagenic agent used. (29 Refs)

37. THE THYMIDINE INCORPORATION INHIBITING SCREENING SYSTEM (TTS) TO TEST CARCINOGENIC SUBSTANCES (A NUCLEAR DNA SYNTHESIS SUPPRESSIVE SHORT TERM TEST).

Amlacher E, Rudolph C
Inst. Pathology, Friedrich Schiller Univ., Ziegelmuhlenweg 1, 6900 Jena, E. Germany
Arch Geschwulstforsch; 51(7):605-610 1981

A short-term screening test is described in which the effects of carcinogens on DNA synthesis were measured by the determination of the mean number of silver grains per nucleus in the renal tubule and liver epithelia of 14-day-old CBA mice following ip injection of carcinogen. Fifteen hr after the injection of 0.1 ml of the dissolved chemical in a concentration representing 15/30% of the LD50, 3H-thymidine was injected ip. Autoradiographs of the nuclei of the renal tubular epithelia and of the liver epithelium were examined by visual silver grain counting. From this test, it was demonstrated that carcinogenic compounds of several different chemical classes (nitrosated amines, azo dyes, azo compounds, aliphatic iso- and heterocycles, aromatic amines, and metallic ions) partially inhibited the nuclear incorporatio n of thymidine in a significant manner over a time period longer than 24 hr. This decrease was expressed as a decrease of the mean of the silver grain number per nucleus in comparison with unaltered controls. This decrease was used as a criterion for the suppressive effect of carcinogenic substances on the rate of nuclear DNA synthesis. No false-positive results were obtained for noncarcinogenic compounds. The effectiveness of this test is discussed. (6 Refs)

38. EFFECTS OF HARMAN AND NORHARMAN ON THE METABOLISM OF ANILINE AND P-DIMETHYLAMINOAZOBENZENE.

Hayashi K
Dept. Public Health, Jikei Univ. Sch. Medicine, Tokyo, Japan
Nippon Eiseigaku Zasshi; 36(2):495-505 1981

The metabolism and mutagenicity of aniline and p-dimethylaminoazobenzene (p-DAB) were studied in vitro using rat liver microsomes. In the absence of harman (l-methyl-9H-pyrido[3,4-b]indole) and norharman (9H-pyrido[3,4-b]indole), p-DAB was metabolized to aniline without accumulation of p-methylaminoazobenzene (p-MAB) or p-aminoazobenzene (p-AAB). Aniline was metabolized to p-aminophenol (p-AP). Harman or norharman substantially inhibited metabolism of aniline to p-AP in microsomes. Norharman was a greater inhibitor than harman. Norharman slightly reduced the metabolism of p-DAB to aniline and caused the accumulation of p-DAB, p-MAB, and p-AAB. The metabolites of aniline, o-aminophenol, m-aminophenol, p-AP, and nitrosobenzene, were tested for mutagenicity in Salmonella typhimurium TA98. Nitrosobenzene was mutagenic only in the presence of norharman with S-9 mix. Similarly p-MAB, p-AAB, and aniline were mutagenic in TA98 only in the presence of norharman with S-9 mix. Harman and norharman each greatly inhibited aniline hydroxylase activity, while aminopyrene demethylase had only a slight effect. Aryl hydrocarbon hydroxylase was inhibited by norharman, but not by harman. (23 Refs) (In JPN)

CELLULAR EFFECTS OF NITROSO COMPOUNDS

39. COMPARISONS OF THE EFFECTS OF CHEMICAL CARCINOGENS IN MIXED CULTURES OF RAT HEPATOCYTES AND HUMAN FIBROBLASTS.

Strom S, Kligerman AD, Michalopoulos G
Dept. Pathology, Duke Univ. Medical Center, Durham, NC, 27710
Carcinogenesis; 2(8):709-715 1981

Human male diploid fibroblasts (strain GM 3468) and parenchymal hepatocytes from male Sprague Dawley rats were treated separately and in mixed cell cultures with benzo[a]pyrene (BP), diethylnitrosamine (DEN), or 2-acetylaminofluorene (AAF). Fibroblast DNA was prelabeled with 5-bromo-2'-deoxyuridine. After exposure to the carcinogens, fibroblast and hepatocyte DNA was analyzed for unscheduled DNA synthesis (UDS). Fibroblast and hepatocyte DNA from mixed cultures was separated by isopycnic centrifugation in neutral cesium chloride. The hepatocarcinogens DEN and AAF produced increased UDS in hepatocytes, but not in fibroblasts, either separately or in mixed cultures. BP, a non-hepatocarcinogen, produced more UDS in fibroblasts than in hepatocytes in mixed cultures. More BP was bound to fibroblast DNA than to hepatocyte DNA. BP bound to DNA from cultures of fibroblast alone was about 30% of that bound to fibroblast DNA from mixed cultures. BP produced no UDS in fibroblast in the absence of hepatocytes. Evidently the hepatocytes activated the UDS-promoting capacity of BP, which then was passed to the fibroblasts. The results obtained with BP, DEN, and AAF correspond to previous in vivo observations of the tissue-specific carcinogenicity of the three agents. The possibility that intercellular distribution may play a role in carcinogenic effects is indicated. (37 Refs)

40. PROTECTIVE ROLE OF THE GLUTATHIONE REDOX CYCLE AGAINST ADRIAMYCIN-MEDIATED TOXICITY IN ISOLATED HEPATOCYTES.

Babson JR, Abell NS, Reed DJ
(c/o Reed) Dept. Biochemistry and Biophysics, Oregon State Univ., Corvallis, OR, 97331
Biochem Pharmacol; 30(16):2299-2304 1981

Incubation of isolated rat hepatocytes with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) resulted in the selective and extensive (greater than 90%) inactivation of glutathione reductase. BCNU also depleted intracellular glutathione by 70% but had no significant effect on cell viability or lipid peroxidation. Incubation of BCNU-treated hepatocytes with adriamycin (ADR) resulted in a decrease in cell viability concurrent with an increase in lipid peroxidation. These effects were not observed with untreated hepatocytes incubated with ADR. Glutathione depletion with diethylmaleate and incubation with ADR did not result in a significant decrease in cell viability or increase in lipid peroxidation. Incubation of BCNU-treated hepatocytes with ADR in the presence of exogenous alpha-tocopherol resulted in a significant amount of protection from ADR-mediated damage. (Author abstract) (47 Refs)

41. EFFECT OF ANTINEOPLASTIC AGENTS ON THE PROLIFERATIVE ACTIVITY OF HUMAN BREAST CANCER CELLS CULTURED IN VIVO IN THE DIFFUSION CHAMBERS.

Shamaev VI, Krutova TV, D'iachkovskaia RF, Korman DB
Section Kinetics of Chemical and Biological Processes, Inst. Chemical Physics, Moscow, USSR
Biull Eksp Biol Med; 91(7):77-79 1981

To evaluate the effect of thiophosphamide, methylnitrosourea, and diazane on proliferation of tumor cells, surgery specimens were placed in the diffusion chambers, which were implanted into the abdominal cavity of CBA mice. On day 3-7 after the implantation, animals received single ip injection of antineoplastic agent at the max tolerant doses. All three agents caused marked inhibition of mitotic index in cultured breast cancer cells. (11 Refs) (In RUS)

IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS

42. A SURVEY OF ETHYLNITROSOUREA-INDUCED RAT GLIOMAS FOR THE PRESENCE OF TUMOUR REJE CTION ANTIGENS EXPRESSED IN VIVO.

Spence AM, Priestley G
RG-20 Neurology, Univ. Washington, Seattle, WA, 98195
Neuropathol Appl Neurobiol; 7(1):63-75 1981

Seven malignant gliomas induced in F-344 rats with transplacentally-induced ethylnitrosourea (ENU) using conventional transplantation assays were tested for tumor rejection antigens. Assay for tumor rejection antigens of syngeneic rats was attempted by ligation or excision of tumor grafts, or by inoculation of radiation-killed tumor cells or live tumor cells at sublethal doses. Groups were then challenged with viable tumor cells and tumor outgrowth compared to that in control groups. In 4/5 cell lines the tumor ligation method was unusable because of high incidence of local tumor recurrences or metastases. Heavily irradiated cell suspensions exposed to 60Co

(15,000 rad) were used for immunization of six of the glioma lines. Despite the irradiation, inocula produced palpable nodules before regression. After a series of immunizing injections, challenge was performed 7-18 days after the last immunization. The outgrowths in two cases (a cerebral glioblastoma and cerebral mixed astrocytoma-ependymoma) indicated tumor rejection responses. Immunization with a mixed oligodendroglioma-astrocytoma and two glioblastoma multiforme led to enhanced outgrowth of challenge cell inocula. The remaining two tumors, a glioblastoma multiforme and a mixed astrocytoma-oligodendroglioma, showed neither rejection nor enhancement response. Immunization with a 3-methylcholanthrene-induced urinary bladder carcinoma line had no effect on the outgrowth of six of the glioma cell lines. ENU-induced malignant rat gliomas apparently do not uniformly elicit strong tumor rejection responses in vivo. (42 Refs)

43. SYNGENEIC IMMUNE RESPONSE TO RAT TRACHEAL EPITHELIAL CELLS TRANSFORMED IN VITRO BY N-METHYL-N-NITRO-N-NITROSOGUANIDINE.

Braslawsky GR, Steele V, Kennel SJ, Nettesheim P
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Br J Cancer; 44(2):247-257 1981

Two cell lines (2-10-1 and 8-10-2) derived by exposure of primary tracheal explants to MNNG in vitro were not tumorigenic in syngeneic F-334 rats or athymic BALB/c (nu/nu) mice at early passage, but became tumorigenic at late passage. These cell lines are therefore suited to study the expression of neoantigens during neoplastic development. Transplantation resistance to late-passage, tumorigenic cells was induced in syngeneic rats using an immunization protocol of repeated cell inoculation and tumor ablation. Spleen cells from such animals were reactive in 20h microcytotoxicity assays against neoplastic cell lines, but unreactive to normal tracheal epithelial cells. Similarly, immune spleen cells co-cultivated in vitro for 6 days with irradiated neoplastic cell lines before assay for microcytotoxicity were strongl y reactive, whereas co-cultivation with normal epithelial cells did not stimulate reactivity. Antibody to these neoplastic cell lines was demonstrated in sera of tumor-resistant rats by an indirect radiolabeled-antibody binding test and by indirect immunofluorescence. There was no significant binding to normal tracheal epithelial cell outgrowths. (Author abstract) (28 Refs)

44. PRESENCE OF ANTI-GAMMA-FA-REACTIVE ANTIGENS IN SPONTANEOUS AND CARCINOGEN-INDUCED MALIGNANCIES OF EXPERIMENTAL ANIMALS.

Higgins PJ, Tong C, Borenfreund E
Lab. Cell Biochemistry, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Oncology; 38(6):340-345 1981

Immunochemical analysis of various tumors, representing 12 different tissue sites of origin, revealed a gamma-fetal antigen(gamma-FA)-like component in 17 of 23 malignant neoplasms of the mouse. This antigen was identified in extracts of spontaneous and carcinogen-induced murine tumors as well as in extracts of hepatic tumors initiated in the rat with diethylnitrosamine. The occurrence of gamma-FA in 75% of the malignant tumors examined and its presence in the sera of rodents bearing transplanted and primary cancers suggests an associative relationship of potential diagnostic value. This possibility is supported by the observation that immunoprecipitable gamma-FA appeared in the sera of hepatocarcinogen-treated rats several wk prior to the detection of alpha-fetoprotein. (Author abstract) (26 Refs)

45. VIRUSES AS COFACTORS IN CHEMICAL CARCINOGENESIS.

Fey F
Zentralinstitut fur Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 51(7):611-614 1981

The interaction between viruses and chemical carcinogens was studied in mice. Newborn XVII mice were administered cell-free endogenous virus isolate from the thymus, lymph nodes, bone marrow, and spleen of mice with nitrosomethylurea (NMU)-induced leukemia; 1 wk later a suboptimal dose of NMU (50 ug) was given (Group I). Two control groups were treated either with the cell-free isolate (Group II) or with the suboptimal NMU dose (Group III). The animals which survived were killed after 16 mo to prevent occurrence of spontaneous leukemia. The number of animals with leukemia and tumors was 35/72 (48.6%) in Group I, 5/38 (13.2%) in Group II, and 3.31 (9.7%) in Group III. The frequency of neoplasms is significantly higher in Group I than in Groups II and III. The latent period was 388 days in Group I, 464 days in Group II, and 462 days in Group III. The findings were confirmed in a similar experiment with C57Bl x BALB/C hybrid mice with an extremely low incidence of spontaneous leukemia: the tumor incidence was 3x higher after combined treatment with virus isolate and the carcinogen than after treatment with virus isolate and the carci nogen than after treatment with either one alone. The findings indicate the synergistic effects of viruses and chemical carcinogens in the murine system. (14 Refs) (In GER)

EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS

46. EPIDEMIOLOGICAL ASPECTS OF ESOPHAGEAL CANCER.

Ruggieri M, Tosato F, De Rocco K, Lepore M, Cipriano E, Paolini A
IV Cattedra di Clinica Chirurgica Generale e Terapia Chirurgica, Universita degli Studi di Roma, Rome, Italy
Recenti Prog Med; 70(5):545-556 1981

The epidemiology of esophageal cancer (EC) is reviewed and epidemiological data are presented for a series of patients subjected to surgery for EC at a clinic during the period 1971-1980. The factors probably favorable for the development of EC are ethyl alcohol, tobacco, polycyclic aromatic hydrocarbons (benzopyrene, dibenzanthracene, and 3-methylcholanthrene) present in smoked foods, nitrosamines, molybdenum, tannin, hot food, diet deficient especially in thiamine, riboflavine, and vitamin C, esophageal stenosis, peptic reflux esophagitis, brachyesophagus, achalasia of the cardia, gastric resection, and Plummer-Vinson syndrome. The epidemiological analysis of the patients treated during the 1971-1980 period showed that all patients were in the age bracket 42-75 with a mean of 59.3 yr, and that women accounted for 5.2% of the patients only. Alcohol consumption (1 liter/day) was established in 18.5% of the patients, alcohol consumption and smoking (10 or more cigarettes/day) in 52.5%, smoking only in 18.5%, and neither smoking nor alcohol consumption in

10.5%. The cervical third of the esophagus was affected in 10.5% of all cases, the thoracic third in 34%, and the abdominal third in 55.5%. (28 Refs) (In ITA)

47. THE RESPIRATORY EPITHELIUM. IX. VALIDITY AND REPRODUCIBILITY OF REVISED CYTOLOGIC CRITERIA FOR HUMAN AND HAMSTER RESPIRATORY TRACT TUMORS.

Hess FG, McDowell EM, Resau JH, Trump BF
Food and Drug Res. Lab., Waverly Res. Center, P.O. Box 107, Waverly, NY, 14892
Acta Cytol (Baltimore); 25(5):485-498 1981

Cytologic criteria, based upon features of differentiation at the cellular level, have been established previously for human and hamster respiratory tract tumors. In order to validate these histogenetic revised criteria and to study their reproducibility, imprint smears of human and hamster tumors, hamster tracheal washing specimens and preoperative human specimens of sputa, bronchial washings and bronchial brushings were coded randomly, followed by blind cytologic study of the tumor cells. The hamster tumors were induced by intratracheal instillation of benzo(a)pyrene-ferric oxide or sequential administration of benzo(a)pyrene-ferric oxide and N-methyl-N-nitrosourea. Greater accuracy and reliability were obtained for the histogenetic cytodiagnosis versus the histogenetic histologic evaluation tha n were achieved for the conventional cytodiagnosis versus the World Health Organization histologic evaluation of 1967. The histogenetic classification utilizes diagnostic criteria that may be universally applicable by pathologists and cytopathologists. Many poorly to well-differentiated epidermoid carcinomas, poorly to well-differentiated adenocarcinomas, large-cell carcinomas and giant-cell carcinomas, diagnosed as such by conventional cytologic criteria, possessed histogenetic criteria of combined epidermoid and adenocarcinomas. The new data clarify conventional cytodiagnoses of poorly differentiated epidermoid carcinomas and poorly differentiated adenocarcinomas and eliminate vague categories, such as large-cell undifferentiated, giant-cell and small-cell anaplastic carcinomas. (Author abstract) (40 Refs)

48. DETECTION OF NITROSAMINES IN A COMMONLY USED CHEWING TOBACCO.

Bhide SV, Pratap AI, Shivapurkar NM, Sipahimalani AT, Chadha MS
Cancer Res. Inst., Bombay 400 012, India
Food Cosmet Toxicol; 19(4):481-483 1981

Ethanol and acetone-water extracts were made from Pandharpuri, a brand of chewing tobacco popular in India. The extracts were analyzed by thin layer chromatography (TLC), high pressure liquid chromatography (HPLC), and gas chromatography using a thermal energy analyzer (GLC-TEA). HPLC revealed the presence of n-nitrosodimethylamine (NDMA) (2 ug/g tobacco), N-nitrosohydroxyproline (NHPRO) (1 ug/g), as well as N-nitrosopyrrolidine (NPYR) and n-nitrosonornicotine (NNN). GLC-TEA confirmed the presence of NDMA (2-3 ug/g), NPYR (1-2 ug/g), and NNN (1 ug/g). The presence in tobacco of substances known to cause cancer in laboratory animals suggests the need for further research on their effects on habitual users of chewing tobacco and a possible relationship to cancer of the upper digestive tract in humans. (21 Refs)

REVIEWS INCLUDING NITROSO COMPOUNDS

49. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.

International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

Eighteen monographs present experimental and human data for the following antineoplastic and immunosuppressive agents: 5-azacytidine, azathioprine, bischloroethyl nitrosourea, bleomycins (sulfates and hydrochlorides), chlorambucil, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, cisplatin, cyclophosphamide, dacarbazine, 5-fluorouracil, isophosphamide, 6-mercaptopurine, methotrexate, prednisone, procarbazine hydrochloride, treosulfan, vinblastine sulfate, and vincristine sulfate. Section 1 of each monograph summarizes chemical and physical properties; Section 2 describes production, use, occurrence, and analysis. Section 3 covers biological data relevant to evaluation of carcinogenic risk in humans, including carcinogenicity studies, toxic effects, metabolic data, mutagenicity and other short-term tests, and when available case reports or epidemiological studies of cancers present in patients treated with the compound. Section 4 summarizes pertinent animal and human data and gives critical views of the IARC Working Group. (1452 Refs)

50. MOLECULAR PHARMACOLOGY PROGRAM.

Tew KD
Div. Medical Oncology, Georgetown Univ. Sch. Medicine, Washington, DC, 20007
Georgetown Med Bull; 34(4):22-23 1981

Nitrogen mustard and nitrosourea destroy cancer tumor cells by interacting directly with their nuclear macromolecules. For clearer understanding of molecular phenomena, which lead to tumor cell death, different projects are under way. One project tries to define mechanism of nitrosourea toxicity in human and murine bone marrow. Another studies interaction of corticosteroids and alkylating agents and has demonstrated that specific nuclear chromatin targets can be sensitized to nitrosourea by preliminary pretreatment with hydrocortisone. Another project examines potential differences between nuclear chromatin structure and function of normal, tumor, and neoplastic cells, which have developed acquired resistance to nuclear-reactant drugs. The most promising study relates to organization of chromatin and chromosomes on a structure framework known as the nuclear matrix and indicates that drug interaction with this matrix may be extremely deleterious to tumor cells. (no Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Abell NS..... 40
Amlacher E..... 37
Andrews JP..... 16
Aoike A..... 20
Archer MC..... 3
Athanasiou K..... 35
Autrup H..... 8
Babson JR..... 40
Beattie CW..... 30
Bereziat JC..... 27
Bhide SV..... 48
Birt DF..... 31
Blackburn GR..... 16
Bohm N..... 29
Borenfreund E..... 44
Braslawsky GR..... 43
Brassow F..... 32
Bruce WR..... 3
Casperson C..... 36
Castegnaro M..... 27
Castegnaro M..... 6
Chadha MS..... 48
Christensen B..... 8
Cipriano E..... 46
Custer RP..... 16
D'iachkovskaia..... 41
Das Gupta TK..... 30
Davaki P..... 26
Davies MH..... 31
De Rocco K..... 46
Denzer U..... 32
DiAugustine RP..... 25
Faiferman I..... 12
Fey F..... 45
Fujimoto S..... 22
Fujita M..... 23
Fukuda S..... 4
Ghosh BC..... 12
Ghosh L..... 12
Grafstrom RC..... 8
Griciute L..... 27
Habs M..... 11
Haines K..... 1
Haines K..... 2
Harrington GW..... 5
Hasunuma M..... 4
Hatayama I..... 15
Hayashi K..... 38
Hayashi M..... 28
Hess FG..... 47
Higgins PJ..... 44
Hirose M..... 28
Hoshi K..... 21
Hoshino K..... 15
House FR..... 1
House FR..... 2
Huang SL..... 36
Huang SM..... 36
Imai F..... 15
Imaida K..... 28
Inaguma H..... 19
Inokuchi H..... 20
Inokuchi K..... 18
International A..... 49
Ishihara Y..... 28
Ito H..... 28
Ito N..... 15
Ito N..... 28
Iwamatsu M..... 18
Izumi T..... 19
Kamano Y..... 19
Kawachi T..... 17
Kawai K..... 20
Kawai K..... 22
Kennel SJ..... 43
Kieler J..... 8
Kiessling M..... 29
Kikugawa K..... 4
Kleihues P..... 29
Kligerman AD..... 39
Korman DB..... 41
Krutova TV..... 41
Kurechi T..... 4
Kurihara M..... 19
Kyrtopoulos SA..... 35
Lantos PL..... 26
Lee L..... 3
Lepore M..... 46
Lijinsky W..... 10
Lijinsky W..... 11
Lijinsky W..... 9
Lindsey WF..... 30
Linnoila RI..... 25
Lipinski R..... 29
Maruyama S..... 19
Matsuguchi T..... 18
Matsukura N..... 17
McDowell EM..... 47
Menjo M..... 21
Michalopoulos G..... 39
Mifuchi I..... 34
Mitschke H..... 32
Miyazaka K..... 19
Morino K..... 17
Morita T..... 34
Murakami T..... 21
Nakajima A..... 21
Nampei S..... 23
Nassauer J..... 12
Nettesheim P..... 25
Nettesheim P..... 43
Nishimura K..... 15
Ohgaki H..... 17
Okui K..... 19
Paolini A..... 46
Parzefall W..... 14
Pignatelli B..... 6
Pool B..... 11
Pour P..... 31
Pour PM..... 24
Pratap AI..... 48
Preussmann R..... 11
Priestley G..... 42
Quast JF..... 13
Rao MS..... 10
Reed DJ..... 40
Reed PI..... 1
Reed PI..... 2
Resau JH..... 47
Reuber MD..... 11
Reuber MD..... 9
Rudolph C..... 37
Ruggieri M..... 46
Saito T..... 18
Sakai A..... 33
Sano C..... 18
Sasaki O..... 18
Sasaki Y..... 19
Sato K..... 15
Sato M..... 23
Sato T..... 15
Sawaki M..... 34
Sayed S..... 31
Scarpelli DG..... 10
Schulte-Hermann..... 14
Shamaev VI..... 41
Shirakabe H..... 19
Shivapurkar NM..... 48
Sipahimalani AT..... 48
Smith PL..... 1
Smith PL..... 2
Sorof S..... 16
Spence AM..... 42
Steele V..... 43
Stott WT..... 13
Strom S..... 39
Stummeyer D..... 11
Sugimoto H..... 22
Sunagawa M..... 21
Suwa B..... 19
Taguchi T..... 23
Takeshita K..... 21
Tanaka Y..... 20
Tanaka Y..... 22
Tanimura A..... 33
Tatematsu M..... 15
Tew KD..... 50
Tomita I..... 33
Tong C..... 44
Tosato F..... 46
Trump BF..... 47
Tsuchida S..... 15
Tsuchihashi Y..... 22
Tsukahara Y..... 23
Uosumi G..... 20
Uozumi G..... 22
Vohra SK..... 5
Walker EA..... 6
Walters CL..... 1
Walters CL..... 2
Watanabe PG..... 13
Waters MD..... 36
Werner B..... 32
Yasui A..... 19
Yoshikawa K..... 33
Ziebarth D..... 7

☆ U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/110

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICOLOGICAL ASPECTS OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH).
De Fernicola NA, De Azevedo FA
Divisao de Toxicologia e Ecotoxicologia, Diretoria de Tecnologia e Desenvolvimento, Sao Paulo, Brazil
Rev Bras Saude Ocup; 33(9):62-68 1981
In POR

2. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.
International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

3. STUDIES ON THE ROLE OF ORAL CONTRACEPTIVE USE IN THE ETIOLOGY OF BENIGN AND MALIGNANT LIVER TUMORS.
Mettlin C, Natarajan N
Cancer Control and Epidemiology, Rosewell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Surg Oncol; 18(1):73-85 1981

RADIATION CARCINOGENESIS

4. EXPERIMENTAL RADIATION CARCINOGENESIS: WHAT HAVE WE LEARNED?
Fry RJ
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Radiat Res; 87(2):224-239 1981

5. INFLUENCE OF NONCARCINOGENIC SECONDARY FACTORS ON RADIATION CARCINOGENESIS.
Little JB
Lab. Radiobiology, Harvard Univ., Sch. Public Health, Boston, MA, 02115
Radiat Res; 87(2):240-250 1981

6. MEDICAL IRRADIATION IN JAPAN - STOCHASTIC RISK ESTIMATION AND ITS REDUCTION.
Hashizume T
Div. Physics, National Inst. Radiological Sciences, 9-1 Anagawa 4-Chome, Chiba Shi 260, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(5):445-474 1981
In JPN

7. RADIOACTIVITY IN DRINKING WATER.
Cothern CR
Office of Drinking Water, Environmental Protection Agency, Washington, DC
Radioactivity in Drinking Water. Available from National Technical Information Service, Springfield, VA, as PB81-192833:, 79 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. EPIDEMIOLOGY OF GASTROINTESTINAL CANCER.
Miller AB
NCIC Epidemiology Unit, Univ. Toronto, McMurrich Building, Toronto, Ontario M5S 1A8, Canada
Compr Ther; 7(8):53-58 1981

9. EPIDEMIOLOGICAL ASPECTS OF ESOPHAGEAL CANCER.
Ruggieri M, Tosato F, De Rocco K, Lepore M, Cipriano E, Paolini A
IV Cattedra di Clinica Chirurgica Generale e Terapia Chirurgica, Universita degli Studi di Roma, Rome, Italy
Recenti Prog Med; 70(5):545-556 1981
In ITA

10. PANCREATIC CANCER.
Cohn I, Hastings PR
Dept. Surgery, Louisiana State Univ., 1542 Tulane Ave., New Orleans, LA, 70112
UICC Tech Rep Ser. Vol. 57, Issue 12, 142 pp., 1981.

11. GENETICALLY DETERMINED SUSCEPTIBILITY TO CANCER.
Marks PA
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Blood; 58(3):415-419 1981

12. ETIOLOGY, ROLE AND DETECTION OF CHROMOSOMAL ABERRATIONS IN MAN.
Fabricant JD, Legator MS
Dept. Preventive Medicine, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
JOM; 23(9):617-625 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

13. INDUSTRIAL CARCINOGENESIS.
Vickers CF
Dept. Dermatology, Univ. Liverpool, Liverpool L69 3BX, England
Br J Dermatol; 105(Suppl21):57-61 1981

14. ENVIRONMENT AND HEALTH (LITERATURE REVIEW).
Khachatrian TS
Dept. Public Health, State Inst. Advanced Training for Physicians, Erevan, USSR
Zh Eksp Klin Med; 21(3):287-292 1981
In RUS

15. LIFESTYLE AND CANCER.
Higginson J
International Agency for Res. on Cancer, Lyon, France
Cancer Forum; 5(1):4-14 1981

16. ASBESTOS, AN ENVIRONMENTAL POLLUTANT.
Zamfir G, Diaconu R
Institutul de igiena si sanatate publica, Iasi, Romania
Igiena; 30(1):1-9 1981
In RUM

17. REVIEW OF UICC PROGRAM ON SMOKING AND LUNG CANCER.
Gray N
Smoking and Cancer Program, UICC, 3 rue du Conseil General, 1205 Geneva, Switzerland
Cancer Forum; 5(1):15-18 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

18. EXPERIMENTAL APPROACHES TOWARDS THE BIOCHEMICAL ANALYSIS OF CHEMICAL CARCINOGENESIS.
Laishes BA
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
ACS Symp Ser; 160:197-215 1981

19. FIBRONECTIN AND RELATED TRANSFORMATION-SENSITIVE CELL SURFACE PROTEINS (ONCOLOGY OVERVIEW).
International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Fibronectin and Related Transformation-Sensitive Cell Surface Proteins (Oncology Overview) Chen, L. B, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923001:; OB-81/01:95pp. 1981

20. PRENEOPLASTIC LESIONS OF THE MAMMARY GLAND. (ONCOLOGY OVERVIEW)
International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Preneoplastic Lesions of the Mammary Gland (Oncology Overview) Medina, D, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923002; OB-81/02:134pp. 1981

21. LYMPHOCYTE DIFFERENTIATION: AN ESSENTIAL BASIS FOR THE COMPREHENSION OF LYMPHOID NEOPLASIA.
Magrath IT
Pediatric Oncology Branch, Div. Cancer Treatment, NCI, NIH, Public Health Service, United States Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 67(3):501-514 1981

MODIFICATION OF CARCINOGENESIS

22. FACTORS STIMULATING AND INHIBITING TUMOR GROWTH IN CARCINOGENESIS.
Kochergina NI, Kosova IP
Res. Lab. Experimental Immunobiology, Moscow, USSR
Usp Sovrem Biol; 91(3):409-418 1981
In RUS

23. TWO INDEPENDENT ASPECTS OF TUMOR PROMOTION.
Berenblum I, Armuth V
Weizmann Inst. Science, Rehovot, Israel
Biochim Biophys Acta; 651(1):51-63 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

24. BURKITT'S LYMPHOMA.
Ziegler JL
NCI, Bethesda, MD, 20205
N Engl J Med; 305(13):735-745 1981

25. REVIEW ARTICLE. REGULATION OF EXPRESSION OF THE INTEGRATED RETROVIRUS GENOME.
Weinberg RA, Steffen DL
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
J Gen Virol; 54(part1):1-8 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

26. THE DEVELOPMENT AND VALIDATION OF MUTAGENICITY SCREENING TESTS.
Durkin PR, Santodonato J
Center for Chemical Hazard Assessment, Syracuse Res. Corporation, Merill Lane, Syracuse, NY, 13210
Tappi; 64(9):153-159 1981

27. SHORT-TERM TEST SYSTEMS FOR POTENTIAL MUTAGENS AND CARCINOGENS: I. MICROBIAL TESTS (ONCOLOGY OVERVIEW).
International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Short-Term Test Systems for Potential Mutagens and Carcinogens: I Microbial Tests (Oncology Overview) Simmon, V F; Peirce, V; eds This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922903:; OK-81/03:124pp. 1981

28. ANIMAL MODELS OF INTRA-ORAL CHEMICAL CARCINOGENESIS: A REVIEW.
Eveson JW
Dept. Oral Medicine and Pathology, Guy's Hosp., London SE1 9RT, England
J Oral Pathol; 10(3):129-146 1981

29. THE CHROMOSOMES IN HEMATOLOGY.
Berger R
Laboratoire de Cytogenetique, Institut de Recherches sur les Leucemies et les Maladies du Sang, UER d'Hematologie, Hopital Sant-Louis, 2 place du Dr. Fournier, 75475 Paris Cedex 10, France
Cancer Genet Cytogenet; 4(1):69-88 1981

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
5285 Port Royal Road
Springfield, Va. 22161

OFFICIAL BUSINESS

Penalty for Private Use, $300

PRINTED MATTER

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF COMMERCE
COM-211

THIRD CLASS
BULK RATE

U.S.MAIL

CK-01

CANCERGRAMS are distributed for the International Cancer Research Data Bank (ICRDB) by the National Technical Information Service (NTIS). CANCERGRAMS are available from NTIS on a standing order basis at $2 each for North American Continent addressees and $3 each for other addressees. An NTIS deposit account is required. For a list of subject categories or other information, please write to:

Subscription Section
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161

NOTICE OF MAILING CHANGE

☐ Check here if you wish to discontinue receiving this publication.

☐ Check here if your address has changed and you wish to continue receiving this publication. (Be sure to furnish your complete address including zip code.)

Tear off cover with address label still affixed and send to:

Computer Support Center
ICRDB Program
IIT Research Institute
10 West 35th Street
Chicago IL. 60616

CK 01/82/03

NCI/ICRDB/CK01 82/03 PB82-935103

ICRDB CANCERGRAM

CHEMICAL CARCINOGENESIS

Nitroso Compounds

SERIES CK01 No. 82/03 MARCH, 1982

This Cancergram is a service of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM of the U.S. National Cancer Institute. Every few weeks, an updated Cancergram containing abstracts of selected cancer-related articles recently published in more than 3000 journals, and dealing with the topic indicated by the above title, is sent to researchers working in this area. These researchers are identified on the basis of the description of their current research project that has been submitted to the ICRDB Program, directly or via granting agencies.

This Cancergram is prepared by the Cancer Information Dissemination and Analysis Center (CIDAC) for Carcinogenesis Information. ***If this Cancergram is useful and valuable, please send your comments to the CIDAC address below, since future editions depend on user satisfaction and user needs:***

CIDAC FOR CARCINOGENESIS INFORMATION
SCIENCE INFORMATION SERVICES
FRANKLIN INSTITUTE RESEARCH LABORATORIES
20TH AND RACE STREETS
PHILADELPHIA, PA 19103

NEWARK PUBLIC LIBRARY

MAR 30 1982

U. S. GOVT. PUBS.
DEPOSITORY 376

STAY UP TO DATE IN YOUR FIELD. AN AUTOMATIC SDI IN CANCERLIT CAN GIVE YOU A MONTHLY LIST OF NEW ABSTRACTS RETRIEVED BY A CUSTOMIZED SEARCH PROFILE. CONTACT YOUR LIBRARIAN OR THE ICRDB PROGRAM, WESTWOOD BLDG., RM. 10A18, BETHESDA, MD. 20205.

In this issue:

- **FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS..... 1**
- **METABOLISM OF NITROSO COMPOUNDS..... 2-6**
- **INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS..... 7-18**
- **MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS..... 19-29**
- **MUTAGENICITY OF NITROSO COMPOUNDS..... 30-40**
- **CELLULAR EFFECTS OF NITROSO COMPOUNDS..... 41-51**
- **TRANSPLACENTAL EFFECTS OF NITROSO COMPOUNDS..... 52**
- **EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS..... 53-56**
- **REVIEWS INCLUDING NITROSO COMPOUNDS..... 57**

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20.3173/2:

FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS

1. PEROXIDASE ACTIVATION OF N-OH-AAF BY RAT MAMMARY GLAND PARENCHYMAL CELLS (MEETING ABSTRACT).

Wong PK, Hampton MJ, Floyd RA
Oklahoma Medical Research Foundation, Oklahoma City, OK
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Rat mammary gland parenchymal cells activate N-hydroxy-2-acetylaminofluorene (N- OH-AAF) to 2-nitrosofluorene (NOF) and N-acetoxy-2-acetylaminofluorene (N-OAC-AAF) via a nitroxyl free radical form of the carcinogen. Prostaglandin synthetase has a peroxidase activity and hence we have examined parenchymal cells to determine if the activation of N-OH-AAF in the cells occurs by this route. Freshly isolated cells activate N-OH-AAF to NOF as detected by high pressure liquid chromatography (HPLC). Cells frozen at-60C are more active. N-OH-AAF activation appears to be peroxidative since ascorbate and p-aminophenol completely inhibit NOF formation. Neither the acyl-transferase nor deacylase route occurs to any appreciable extent in the cells. Exogenously added arachidonate enhances N-OH-AAF activation and the inhibitor 5,8,11,14-eicosatetraynoic acid (ETYA) considerably decreased N-OH-AAF activation while indomethacin or aspirin were not effective. Ram seminal vesicle microsomes activate N-OH-AAF apparently by prostaglandin synthetase. Our work indicates that N-OH-AAF was activated by lipoxygenase pathway in these cells. The 12L-hydroperoxy-5,8,10,14-icosatetraenoic acid (12-HPETE) generated through endogenous or exogenous arachidonate sources probably is the hydroperoxide substrate for the peroxidase. Platelets which are rich in lipoxygenase also activate N-OH-AAF. Since 12-HPETE is one of the three hydroperoxides found in animal kingdom, the peroxidase activation may have significant importance in mammary gland carcinogenesis. (no Refs)

METABOLISM OF NITROSO COMPOUNDS

2. ALPHA-HYDROXYLATION PATHWAY IN THE IN VITRO MFTABOLISM OF CARCINOGENIC NITROSAMINES: N-NITROSODIMETHYLAMINE AND N-NITROSO-N-METHYLANILINE.

Kroeger-Koepke MB, Koepke SR, McClusky GA, Magee PN, Michejda CJ
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Proc Natl Acad Sci USA; 78(10):6489-6493 1981

Evolution of 15N2-labeled molecular nitrogen was used to gauge the extent of alpha-hydroxylation during rat liver homogenate metabolism of doubly 15N-labeled N-nitrosodimethylamine (DMN) and N-nitrosomethylaniline (NMA). These measurements were correlated with the extent of total metabolism as measured by the disappearance of nitrosamines and by the formation of formaldehyde. The results indicate that approx 34% of DMN and 19% of NMA were metabolized by the alpha-hydroxylation pathway. Positive controls utilizing doubly 15-labeled N-nitroso-N-methylurea yielded 96% of labeled nitrogen. These results are in variance with previously published data which claimed that either less than 5% or about 100% of DMN is metabolized by the route in vitro. Formaldehyde formation was shown to be a poor measure of the extent of metabolism. Semicarbazide gave rise to both formaldehyde and nitrogen, which makes it an undesirable component of the in vitro metabolism mixtures, particularly when those two substances are being meas ured. (Author abstract) (32 Refs)

3. URINARY METABOLITES OF N-NITROSODIPROPYLAMINE, N-NITROSO-2-HYDROXYPROPYLPROPYLAMINE AND N-NITROSO-2-OXOPROPYLPROPYLAMINE IN THE RAT.

Leung KH, Archer MC
(c/o Archer) Dept. Medical Biophysics, Univ. Toronto, Ontario Cancer Inst., 500 Sherbourne St., Toronto, Canada, M4X 1K9
Carcinogenesis; 2(9):859-862 1981

Male Sprague-Dawley rats in groups of two animals each were inoculated ip with N-nitrosodipropylamine (NDPA: 77 mg/kg), N-nitroso-2-hydroxypropylpropylamine (NHPPA: 86 mg/kg), or N-nitroso-2-oxopropylpropylamine (NOPPA: 85 mg/kg). In each case, the major urinary metabolite was the beta-glucuronide of NHPPA. Exhaustive hydrolysis of 24-hr urine samples with beta-glucuronidase yielded conjugated NHPPA in amounts corresponding to 5%, 80%, and 50% of the administered doses of NDPA, NHPPA, and NOPPA, respectively. Levels of unchanged nitrosamines and their metabolites (NHPPA for administered NDPA or NOPPA were generally low: less than 2% of the administered dose). N-nitrosomethylpropylamine and N-nitrosodimethylamine were not detected in any urine samples. (22 Refs)

4. THE FORMATION OF N-NITROSOMETHYL(2-OXOPROPYL)AMINE FROM N-NITROSOBIS(2-OXOPROPYL)AMINE IN VIVO.

Lawson TA, Helgeson AS, Grandjean CJ, Wallcave L, Nagel D
Eppley Inst. Res. Cancer 0613, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB, 68105
Carcinogenesis; 2(9):845-849 1981

Tissue concentrations of N-nitrosobis(2-oxopropyl)amine (BOP) and its metabolites in male Syrian golden hamsters given a single dose of BOP (10 mg/kg, sc) were analyzed by gas chromatography. BOP concentrations were higher in the pancreas than in the liver or salivary glands. N-nitrosomethyl(2-oxopropyl)amine (MOP) was present in higher concentrations in the pancreas than in the liver, and N-nitroso(2-hydroxypropyl)(2-oxopropyl)amine also was preferentially taken up by the pancreas. The results strongly suggested that MOP is a proximate carcinogenic metabolite of BOP. (15 Refs)

5. METABOLIC FATE OF N-METHYL-N-DODECYLNITROSAMINE IN THE RAT, IN RELATION TO ITS CARCINOGENICITY TO THE URINARY BLADDER.

Suzuki E, Mochizuki M, Okada M
Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan
Gan; 72(5):713-716 1981

The metabolic fate of N-methyl-N-dodecylnitrosamine (MDN) was investigated in the rat, in order to elucidate a possible correlation between urinary metabolites and organotropic carcinogenicity to the urinary bladder of this N-nitrosamine. MDN was extensively metabolized in the rat, no unchanged MDN being found in the urine. The urinary metabolites identi-

fied were N-methyl-N-(3-carboxypropyl)nitrosamine (MCPN), N-methyl-N-(2-hydroxy-3-carboxypropyl)nitrosamine, N-methyl-N-(carboxymethyl)nitrosamine, and N-methyl-N-(2-oxopropyl)nitrosamine. Thus the metabolic pattern of MDN was essen tially similar to that of N-methyl-N-(4-hydroxybutyl)nitrosamine, a potent bladder carcinogen, in the rat. A possible important role of MCPN in the induction of bladder tumors by MDN is discussed. (Author abstract) (21 Refs)

6. COMPREHENSIVE ANALYSIS OF URINARY METABOLITES OF N'-NITROSONORNICOTINE.

Hecht SS, Lin D, Chen CB
Div. Chemical Carcinogenesis, Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Carcinogenesis; 2(9):833-838 1981

Urinary N'-nitrosonornicotine (NNN) metabolites in male F-344 rats, male Syrian golden hamsters, and male A/J mice were quantified by high-pressure liquid chromatography. In F-344 rats injected with NNN (3-300 mg/kg), the main urinary products were hydroxy acid (37.2-53.3% of the administered dose), NNN-1-oxide (6.7%-10.7%), norcotinine (3.2-5.1%), keto acid (31.1%-12.8%), and NNN (3.3%-5.2%). Despite the differing organ specificity of NNN in the three species, urinary metabolites in mice and hamsters were qualitatively similar to those in rats. In each case, a marked capacity for 2'- and 5'-hydroxylation was observed. The in vivo metabolites resulting from 2'-hydroxylation of NNN by rat liver microsomes were myosmine and keto alcohol; both gave rise to keto acid as the major urinary metabolite. Lactol, the product of microsomal 5'-hydroxylation, gave hydroxy acid as its major urinary metabolite. The two major metabolites are probably reliable indicators of NNN alpha-hydroxylation in vivo. (19 Refs)

INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS

7. DIFFERENCES IN EXPERIMENTAL PANCREATIC CARCINOGENESIS INDUCED BY ORAL OR SUBCUTANEOUS ADMINISTRATION OF 2,2'-DIHYDROXYDI-N-PROPYLNITROSAMINE IN DUCT-LIGATED HAMSTERS.

Ruckert K, Pracht B, Kloppel G
Dept. Surgery, Univ. Mainz, Langenbeckstrasse 1, D-6500 Mainz, W. Germany
Cancer Res; 41(11,part1):4715-4719 1981

After ligation of the main pancreatic duct in the splenic lobe, Syrian golden hamsters were treated, either po or sc, for 15 wk with dihydroxydi-n-propylnitrosamine for induction of pancreatic duct carcinomas. The incidence, location, and type of proliferative lesions distal and proximal to the ligature were recorded and compared to those of dihydroxydi-n-propylnitrosamine-treated hamsters without duct ligation. Proliferative duct lesions, including carcinomas, developed on either side of the ligation. While after sc administration the incidence was similar to that in nonligated animals, a markedly decreased incidence was found in po-treated animals with duct ligation. The data suggest that the blood stream might be one major access route of the carcinogen to the pancreatic duct cell. Furthermore, it is assumed that an unimpaired release of pancreatic juice in the duodenum is necessary for the enteral resorption of dihydroxydi-n-propylnitrosamine. (Author abstract) (16 Refs)

8. NITROSAMINE-INDUCED TRANSPLANTABLE PANCREATIC DUCTAL ADENOCARCINOMA IN INBRED SYRIAN HAMSTERS.

Sindelar WF, Kurman CC
Surgery Branch, Div. Cancer Treatment, NCI, NIH, United States Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 67(5):1093-1100 1981

A pancreatic ductal carcinoma, designated CBP, was established as a transplantable tumor line in the CB/SsLak inbred strain of Syrian golden hamsters. The tumor, a primary one induced by chronic administration of the nitrosamine N-nitrosobis(2-hydroxypropyl)amine, is a well-differentiated adenocarcinoma that can be propagated by transplantation in syngeneic hamsters. It grows poorly in other hamster strains. The CBP tumor develops in a predictable quantitative manner and metastasizes to regional lymph nodes. Excision of primary transplanted tumor nodules leads to immunity against subsequent secondary tumor challenges. The CBP tumor appears to be a suitable model for biologic and immunologic studies of pancreatic carcinoma in the Syrian hamster. (Author abstract) (21 Refs)

9. THE EFFECT OF THE PANCREATIC CARCINOGEN N-NITROSO-2-METHOXY-2,6,-DIMETHYL-MORPHOLINE ON ENDOCRINE AND EXOCRINE PANCREAS OF SYRIAN HAMSTERS (MEETING ABSTRACT).

Pour PM
The Eppley Institute for Research in Cancer, Omaha, NE
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. The Congress 92 pp., 1981.

All nitrosamines with a pancreatic carcinogenic effect of Syrian hamsters have a common metabolite, N-nitroso(-2-hydroxypropyl) (2-oxopropyl)amine (HPOP). As the cyclic structure of this metabolite, resembling the pyranose form of the hexose-sugars and the sugar moeity of the Streptozocin (SZ), may be responsible for its affinity for the pancreas, we studied the effect of N-nitroso-2-methoxy-2,6-dimethyl nitrosomorpholine (MeNDNM), a fixed cyclic form of HPOP. We found that a single high dose of this compound exhibited, compared to the effect of SZ, selective necrosis of the B-cells of pancreatic islets within 3 days. In surviving hamsters the islets showed signs of regeneration, which was completed within 60-72 hr. Some 40 wk later, however, and in contrast to the effect of SZ, almost all treated hamsters developed pancreatic ductular and mixed ductular-insular tumors. On the other hand, weekly application of MeNDNM in subdiabetogenic induced equivalent tumors, but did not appear to affect islet cells. These results point to the mutual response of the endocrine and exocrine pancreas to this compound, thus indicating the importance of the carcinogen's cyclic structure. Possible mechanisms involved in pancreatotropic effects of this class of chemical carcinogens will be discussed. (no Refs)

10. BLADDER CARCINOGENESIS IN MICE INDUCED BY N-BUTYL-N-(4-HYDROXYBUTYL)NITROSAMINE AND N-ETHYL-N-(4-HYDROXYBUTYL)NITROSAMINE WITH REFERENCE TO THE EFFECT OF CYCLOPHOSPHAMIDE.

Numoto S, Yoshida M, Otsuka H
Second Dept. Pathology, Sch. Medicine, Tokushima Univ., Kuramoto-cho 3-18-15, Tokushima 770, Japan
Gan; 72(5):647-654 1981

The carcinogenicities of N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) and N-ethyl-N-(4-hydroxybutyl)nitrosamine (EHBN) on the urinary bladder were compared in male BALB/c mice. The effect of cyclophosphamide (CPA) on the carcinogenicities was also investigated. The carcinogenic activity on the bladder mucosa of EHBN was similar to that of BBN, and there was no difference in the growth patterns, histological types or invasive characters of carcinoma induced by BBN and EHBN. Benign or malignant tumors of vascular origin developed in the urinary bladders of 15 mice treated with these carcinogens. The incidence of vascular tumors induced by EHBN was significantly higher than that of tumors induced by BBN. Ip injections of CPA seemed to have no effect in the incidence of bladder carcinomas induced by these carcinogens, or on the development of vascular tumors in the bladder wall induced by EHBN. (Author abstract) (18 Refs)

11. INDUCTION OF CHANGES IN THE PEPSINOGEN CONTENT AND THE PEPSINOGEN ISOENZYME PATTERN OF THE PYLORIC MUCOSA OF THE RAT STOMACH BY SHORT-TERM ADMINISTRATION OF STOMACH CARCINOGENS.

Furihata C, Kodama K, Matsushima T
Dept. Molecular Oncology, Inst. Medical Science, Univ. Tokyo, Shirokanedai, Minato-ku, Tokyo 108, Japan
JNCI; 67(5):1101-1104 1981

Changes in pepsinogen isoenzyme patterns were examined in the pyloric mucosae of the stomachs of noninbred male Wistar rats after short-term administration of gastric carcinogens. N-Methyl-N'-nitro-N-nitrosoguanidine, N-ethyl-N'-nitro-N-nitrosoguanidine, and N-propyl-N'-nitro-N-nitrosoguanidine, which induce stomach cancer in rats, decreased the content of pepsinogen isoenzyme 1 (Pg 1), which was separated by polyacrylamide gel electrophoresis. They also decreased the pepsinogen content of the pyloric mucosa. 4-Nitroquinoline 1-oxide, which induces a low incidence of stomach cancer in rats, rarely decreased the Pg 1 content or the pepsinogen content of the pyloric mucosa, and the incidence of such decreases was not statistically significant. However, diethylnitrosamine and dimethylnitrosamine, which do not induce stomach cancer in rats, did not cause any decrease in pepsinogen content. Ethyl methanesulfonate, a direct-acting carcinogen used as a control, also did not decrease the pepsinogen content. (Author abstract) (15 Refs)

12. COMPARATIVE STUDIES ON THE PRODUCTION OF STOMACH TUMORS FOLLOWING THE INTUBATION OF SEVERAL DOSES OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE IN GERM-FREE AND CONVENTIONAL NEWBORN RATS.

Sumi Y, Miyakawa M
Lab. Germfree Life Res., Nagoya Univ. Sch. Medicine, 65 Tsuruamicho, Showa-ku, Nagoya 466, Japan
Gan; 72(5):700-704 1981

The present work was undertaken to investigate the possible role of microflora in gastric tumorigenesis by the comparison of tumor production between germ-free and conventional male Wistar rats given the same amount of N-methyl-N'-nitro-N-nitrosoguanidine into the stomach by catheter during the newborn period. Only 29% of germ-free rats treated with 450 ug/animal that were killed 300 days after the first intubation had tumors in the stomach, whereas 93% of conventional similarly treated rats had such tumors at the same period, suggesting that the microflora might exert a promoting influence upon stomach tumor production. (Author abstract) (27 Refs)

13. STRUCTURAL ALTERATIONS WITHIN N-NITROSOMETHYLUREA-INDUCED MAMMARY TUMORS AFTER IN VIVO TREATMENT WITH CIS-HYDROXYPROLINE.

Strum JM, Lewko WM, Kidwell WR
Dept. Anatomy, Univ. Maryland Sch. Medicine, 655 West Baltimore St., Baltimore, MD, 21201
Lab Invest; 45(4):347-354 1981

N-Nitrosomethylurea-induced mammary tumors in Buffalo rats were examined ultrastructurally and compared with tumors from rats treated in vivo for 9 days with cis-hydroxyproline (CHP). The tumors from untreated animals were heterogeneous histologically but often had their cells arranged in clusters called pseudolobules. At the periphery of the pseudolobules in control tumors, a few myoepithelial cells showed evidence of basal lamina secretion. Outlining the pseudolobules were many mast cells. Treatment with CHP inhibited the growth of the tumors. It increased the extent of atrophy and regression and also induced cyst-like areas to form within the pseudolobules. These 'pseudocysts' were actually part of the stromal compartment and they sometimes contained multilayered basal lamina and mast cells. The extensive multilayering of the basal lamina observed after CHP-treatment was thought to arise from extensive infoldings as the pseudolobules 'shrank' due to atrophy and loss of cells. The multilayering and cell debris disappeared from the pseudocysts, leaving many spaces bounded by myoepithelial cells. The remaining myoepithelial cells appeared atrophied, but often had an expanded rough endoplasmic reticulum. We did not observe evidence of basal lamina secretion by cells in treated tumors, which correlates with CHP's ability to block Type IV collagen production. (Author abstract) (35 Refs)

14. DNA METHYLATION BY N-NITROSOMETHYLBENZYLAMINE IN TARGET AND NON-TARGET TISSUES OF NMRI MICE.

Kleihues P, Veit C, Wiessler M, Hodgson RM
(c/o Hodgson) Abteilung Neuropathologie, Pathologisches Institut der Universitat Freiburg, Albertstrasse 19, 78 Freiburg, W. Germany
Carcinogenesis; 2(9):897-899 1981

Correlations between initial DNA methylation and preferential sites of tumor induction were examined in adult female

NMRI mice given a single ip injection of 14C-labeled N-nitrosomethylbenzylamine (MBN: 2.5/kg). Weekly applications of such a dose administered by the same route induced forestomach carcinomas and lung adenomas in all experimental animals. Lung and forestomach 7-methylguanine and O(6)-methylguanine levels were considerably lower than hepatic levels, but they were higher than the levels in nontarget tissues. The initial extent of DNA methylation in the esophagus was only 21% abbreviation) less than that in the forestomach. Since po MBN results in tumors in both tissues, the results suggested that a different level of DNA modification is required for tumor induction in these tissues. The reason for the resistance of liver cells to methylating carcinogens remains unclear. (7 Refs)

15. CHROMOSOME STUDIES OF PRENEOPLASTIC TRIGEMINAL NERVE (TGN) TUMORS INDUCED BY ETHYLNITROSOUREA (ENU) (MEETING ABSTRACT).

Haag M, Soukup S
Children's Hospital Research Foundation, Cincinnati, OH, 45229
In Vitro; 17(3):241 1981

A transplacental dose of the carcinogen ENU administered to pregnant rats late in gestation results in a high incidence of neurogenic tumors in the adult offspring. The TGN is a particularly sensitive target tissue developing schwannomas with ENU exposure. Chromosome studies on schwannoma lines show a consistent excess of chromosome number 4 structural or numerical abnormalities. Our studies were designed to examine chromosome changes in TGN target tissue as it develops neoplastic properties in vitro. Tissue from grossly normal TGN was initiated in culture at various times after ENU exposure in utero. At various passages cells from treated and control animals were examined for chromosome constitution, growth in semi-solid agar and growth in host animals. After several passages we have been able to show that cells from cultured newborn brain, and from 30, 60 and 90 day TGN of ENU treated animals form colonies in semi-solid agar. Control lines consistently had normal karyotypes, and were negative in agar and host animal tests. Several cell lines from treated TGN that grew in agar were mosaic 2N/4N with no involvement of number 4 in abnormalities. A cell line from a 90-day-old TGN which was 2N produced a tumor in a host animal. The host tumor was histologically a schwannoma and had a normal 2N karyotype. Cloned lines from semi-solid agar have not shown number 4 involved in abnormalities. (no Refs)

16. METASTATIC TUMOR RESULTING FROM INJECTION OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE-EXPOSED HUMAN FIBROBLASTS IN NUDE MICE (MEETING ABSTRACT).

Kurzepa H, Loper JC, Liwnicz BH
Departments of Microbiology and Pathology, University of Cincinnati Medical Center, Cincinnati, OH, 45267
In Vitro; 17(3):223 1981

We reported recently the neoplastic (injection into nude mice) transformation of human fibroblasts by single exposure to N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). Here, we demonstrate the unusual case of a highly malignant tumor which developed after im injection into nude mouse with 99 days latency period. The tumor was first detected at the site of injection and subsequently in the lymph nodes. It also infiltrated the liver, lungs, spleen and pancreas. Growth, and extent of dissemination to organs was shown to be characteristic of this tumor after serial retransplantation into other nude mice with further metastasis into ovary, soft and muscle tissue. Malignant potential increased in every subsequent retransplant as indicated by shorter latency periods. Another indication of the malignancy of this tumor was in the results of implantation into syngeneic BALB/c hairy (Nu+) mice. Nodules have appeared in 3 of the 4 mice with an av latency of 45 days. This indicates the malignancy of this tumor is sufficient to overcome a competent thymus-derived immune system. This established cell line may serve as a model for research on metastasis at the cellular and molecular level. (1 Ref)

17. RELATIONSHIP BETWEEN THE DOSE OF N-DIMETHYLNITROSAMINE AND ITS CARCINOGENIC EFFECT IN RANA TEMPORARIA - A NEW EXPERIMENTAL ANIMAL IN EXPERIMENTAL ONCOLOGY.

Khudolei VV
Lab. Chemical Carcinogens, N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Biull Eksp Biol Med; 91(8):71-73 1981

Carcinogenic effect of N-dimethylnitrosamine (DMNA) was studied in Rana temporaria. Toads were kept in water containing DMNA at concentrations ranging from 1 to 20 ppm. First tumors were recorded 7.5-9 wk after initiation of the exposure. Av latent period of tumor development and incidence of tumors depended upon DMNA dose (22.1 wk and 15% after exposure to 1 ppm, compared with 9.4 wk and 78% after exposure to 20 ppm). (4 Refs) (In RUS)

18. RECENT CONCEPTS OF INITIATION AND PROMOTION IN CARCINOGENESIS.

Becker FF
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Am J Pathol; 105(1):3-9 1981

This review deals with premalignant liver lesions in rats fed N-2-acetylaminofluorene (AAF) or diethylnitrosamine (DEN), DNA alterations in premalignant lesions, and cellular responses to skin tumor promoters such as tetradecanoylphorbol acetate (TPA). Rats fed four cycles of AAF exhibited persistent hepatic nodules having increased mitotic activity and altered DNA. Similarly, premalignant lesions induced by DEN and phenobarbital showed an increase in altered DNA, which paralleled the increase in risk of hepatoma. The broad effects of tumor promotion consist of the induction of proliferation of an initiated cell population and the appearance of aggregates of altered cells. Tumor promotors such as TPA heighten the mitotic responses in these cells and eventually induce epigenetic programmatic a lterations. (38 Refs)

MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS

19. CANCER INDUCTION AFTER PYLOROPLASTY IN RATS TREATED WITH N-METHYL-N'-NITRO-N-NITROSOGUANIDINE (MNNG) (MEETING ABSTRACT).

Salmon RJ, Deschner EE, Okamura T, DeCosse JJ, Sherlock P
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Gastroenterology; 80(5,part2):1268 1981

Since vagotomy and pyloroplasty are more widely used at the present time and vagotomy by itself has been described in animal models as increasing the number of gastric cancers, the effect of duodenal reflux induced by pyloroplasty on cancer induction was investigated in this study. Wistar male rats (19) received MNNG for 12 wk at a dose level of 83 mg/l in the drinking water to initiate glandular adenocarcinoma of the stomach while 3 rats serving as controls received tap water. At the end of 12 wk a pyloroplasty was carried out in 9 rats having received MNNG (Group I) and in 3 controls (Group III). The remaining 10 MNNG treated (Group II) and 5 controls (Group IV) were not operated. All rats were observed for a total period of 38 wk before being sacrificed. No difference in the incidence of MNNG-induced antral adenocarcinomas was found between the Groups I and II. However, in this model a high incidence of duodenal tumors was observed: the unoperated MNNG treated (Group II) animals showed in situ changes in the duodenum while the pyloroplasty group showed 5 massive invasive adenocarcinomas (Group I). It is concluded that, in this model, pyloroplasty alone does not increase the risk for gastric cancer but increases the risk for duodenal tumors. Pyloroplasty accelerates the gastric evacuation rate which in turn results in insult to the duodenal mucosa. Such a condition may require a higher proliferative rate in the duodenum and increase subsequent formation of malignant tumors. (no Refs)

20. ENHANCEMENT OF THE DIMETHYLNITROSAMINE ACUTE EFFECTS IN RAT LIVER BY PRIOR TREATMENT WITH TRITON WR-1339.

Diaz Gomez MI, Godoy HM, Marzl A, De Ferreyra EC, De Fenos OM, Castro JA
(c/o Castro), Centro de Investigaciones Toxicologicas, Villa Martelli 1603, Pcia de Buenos Aires, Argentina
JNCI; 67(5):1089-1092 1981

Prior administration of Triton WR-1339 (tyloxapol, an anionic surfactant) to noninbred Sprague-Dawley male rats significantly enhanced the intensity of the necrogenic effect of dimethylnitrosamine (DMN) on the liver. This phenomenon was established by determination of NADP+ linked isocitrate dehydrogenase activity in the plasma and by histologic procedures. This enhancing effect was not due to an increase in the levels of DNM that reached the liver, because the content of DMN in the livers of Triton WR-1339-treated or untreated animals at 1 or 3 hr was not significantly different. Triton WR-1339 administrat ion had no effect on DMN liver metabolism to formaldehyde or CO2; in addition, the covalent binding of DMN metabolites to nucleic acids or proteins was not modified by pretreatment with Triton WR-1339. However, in vitro, high concentrations (1 mg/ml) of Triton WR-1339 decreased the intensity of these parameters. This effect disappeared when the concentration was lowered to 0.4 mg/ml. Results are compatible with the hypothesis that the potentiating effects of Triton WR-1339 on liver damage caused by DMN and other hepatotoxins were due to a modification of the response of liver cells to injury. (Author abstract) (22 Refs)

21. THE INFLUENCE OF SODIUM SELENITE ON TUMOR INDUCTION BY METHYLNITROSOUREA (MNU) IN RATS.

Warzok R, Thust R, Mendel J, Herbst C, Eismann C
Inst. Pathology, Ernst Moritz Arndt Univ., Friedrich-Loeffler-Str. 23e, DDR-2200 Greifswald, E. Germany
Arch Geschwulstforsch; 51(6):503-508 1981

The effect of sodium selenite (SS) on tumor induction by methylnitrosourea (MNU)was studied. Three groups of inbred strain WE rats (40 rats/group) were treated. Group I received MNU (20 mg/kg body wt/injection ip) in 20 injections at 4-wk intervals and 4 ppm SS in drinking water for 10 mo beginning with the first injection. Group II received only MNU treatment. Group III received only SS treatment. All animals in Groups I and II died by day 330, when Group III animals were killed. Rats not surviving 100 days were excluded from study. A total of 129 tumors in various sites developed in 39 rats in Group I. Group II showed 108 tumors in 35 rats. The difference between Groups I and II was not significant. No tumors developed in Group III rats. SS did not appear to affect MNU tumor induction. (27 Refs)

22. REVERSIBLE INHIBITION OF RAT HEPATOCYTE PROLIFERATION BY HYDROCORTISONE AND ITS EFFECT ON CELL CYCLE-DEPENDENT HEPATOCARCINOGENESIS BY N-METHYL-N-NITROSOUREA.

Kaufmann WK, Kaufman DG, Rice JM, Wenk ML
(c/o D. Kaufman) Dept. Pathology, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514
Cancer Res; 41(11,part1):4653-4660 1981

The susceptibility of hepatocytes to carcinogenesis in vivo may be influenced by the phase of the cell cycle at which carcinogen-induced damage is incurred. In order to better understand this relationship, hepatic cell proliferation in juvenile male Fischer 344 rats was charted following a two-thirds partial hepatectomy. For hepatocytes, two distinct waves of DNA synthesis occurred which were followed after 6 to 8 hr by waves of mitotic cell division. In contrast to this kinetic pattern, when hydrocortisone was given after the partial hepatectomy, the initial waves of DNA synthesis and mitosis by hepatocytes were each delayed by about 15 hr. In rats not given hydrocortisone, susceptibility to hepatocarcinogenesis by N-methyl-N-nitrosourea was greatest at 20 hr after partial hepatectomy when the peak fraction of proliferating hepatocytes was in the S phase. By shifting the time of onset of DNA synthesis, the hydrocortisone treatments also shifted the time with greatest sensitivity to N-methyl-N-nitrosourea, with hepatocytes in late G1 or S again the most susceptible. Numerous tumors were also induced by N-methyl-N-nitrosourea in extrahepatic tissues, including intestine, Zymbal's gland, nervous system, kidney, odontogenic tissues, and peritesticular mesothelium. The results illustrate the importance of cell proliferation in carcinogenesis and further point to the specific sensitivity of certain cell cycle phases. (Author abstract) (31 Refs)

23. THE ROLE OF ESTROGEN IN HEPATIC NEOPLASIA: AN EXPERIMENTAL MODEL (MEETING ABSTRACT).

Wanless IR, Medline A
Toronto Western Hospital, Toronto, Ontario, Canada
Gastroenterology; 80(5,part2):1354 1981

The administration of estrogens to humans has been associated with the development of benign and malignant hepatocellu-

lar neoplasms. We present here a rat model which demonstrates that stilbestrol (DES) promotes the development of hepatic noeplasms in rats previously initiated with diethylnitrosamine (DEN). Thirty-two male rats (Fisher 344) were given a single dose of DEN (200 mg/kg, ip) followed 4 wk later by DES (5 mg, po) twice weekly for up to 50 wk. Other rats given vehicle only served as controls. DES was stopped at the time of sacrifice or 11-29 wk prior to sacrifice. All rats given both DEN and DES developed grossly visible hepatic hyperplastic nodules, measuring up to 29 mm in diameter, after 20 wk of DES. Rats given DEN alone or DES alone did not develop nodules. Microscopic hyperplastic foci also developed in rats given DEN plus DES or DES or DEN alone. The foci developing in rats given DES were largely reversible on cessation of estrogen therapy. Mitotic activity in foci and nodules was prominent during estrogen therapy but declined markedly after cessation of therapy. Similar promoting activity of ethinylestradiol (0.2 mg twice weekly) in male rats and of DES in female rats was observed. The data indicate that estrogens promote neoplasia, perhaps by increasing hepatocytic mitotic activity thereby allowing previously initiated cells to evolve into neoplastic clones. Although comparison with human disease should be made with caution, the parallels to human oral contraceptive-associated hepatic adenomas and carcinomas is obvious. It is possible that some women have latent 'initiated' cells that are unusually responsive to estrogen. (no Refs)

24. EFFECT OF SOME FATTY ACID METHYL ESTERS ON GASTROINTESTINAL CARCINOGENESIS BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE IN RATS.

Arffmann EJ, Rasmussen KS, Hansen FN
Dept. Pathology, Aalborg Hosp., P.O. Box 561, DK-9100 Aalborg, Denmark
JNCI; 67(5):1071-1075 1981

Methyl linoleate hydroperoxide (MLHP) and native methyl linoleate (ML) were tested for carcinogenicity toward the gastrointestinal (GI) tract in male specific-pathogen-free outbred Wistar rats. N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG) was given in the drinking water in a dose of 20 mg/liter when cocarcinogenic properties of the test substances were to be tested. MLHP and ML were fed by stomach tube and had no effect as complete carcinogens. Given concomitantly with MNNG, ML did not enhance carcinogenesis. MLHP in conjunction with MNNG was the only treatment which, as treatment with MNNG in a dose of 83 mg/liter, led to an increase of GI cancers in animals that died before day 354. Cumulative results after a max of 612 days showed a distribution of GI cancers in favor of the glandular stomach only after MLHP was given with MNNG. (Author abstract) (24 Refs)

25. EFFECT OF INDOMETHACIN ON INTESTINAL TUMORS INDUCED IN RATS BY THE ACETATE DERIVATIVE OF DIMETHYLNITROSAMINE.

Pollard M, Luckert PH
Lobund Lab., Univ. Notre Dame, Notre Dame, IN, 46556
Science; 214(4520):558-559 1981

Over the course of 20 wk, Sprague-Dawley rats developed intestinal tumors in response to an ip injection of the acetate derivative of dimethylnitrosamine. The same agent did not induce tumors in Lobund-Wistar rats. The number of tumors was significantly smaller in rats given drinking water containing indomethacin (beginning 14 days after the injections) than in control rats given drug-free water. (Author abstract) (12 Refs)

26. DRUG SENSITIVITY OF RAT BLADDER CANCER IN SYNGENEIC HOSTS AND ATHYMIC NUDE MICE.

Kitagawa H, Nakamura M, Kiuchi Y, Iwaguchi T
Div. Experimental Animals, Tokyo Metropolitan Inst. Medical Sci., Tokyo, Japan
Gan; 72(5):802-805 1981

The effects of chemotherapeutic agents on BC-47 rat bladder cancer were investigated in nude mice and syngeneic hosts to clarify the influence of host factors on chemotherapy. The BC-47 cancer was rich in stroma and lacked central necrosis in syngeneic ACI/N rats. In contrast, in nude mice it had little stroma and underwent necrosis in the center, and cancer cells proliferated primarily at the periphery in contact with the normal host tissue. The cancer showed similar patterns of sensitivity to bleomycin, 1,3-bis(2-chloroethyl)-1-nitrosourea, 5-fluorouracil, and mitomycin C in both hosts. In contrast, adriamycin and pyranyl secalonic acid D (pyranyl secalonic acid) had different effects in the two hosts, being significantly effective in rats, but ineffective in nude mice. (Author abstract) (6 Refs)

27. EFFECTS OF VARIOUS CHEMICALS INCLUDING BILE ACIDS AND CHEMICAL CARCINOGENS ON THE INHIBITION OF METABOLIC COOPERATION.

Noda K, Umeda M, Ono T
Tissue Culture Lab., Yokohama City Univ. Sch. Medicine, Urafune-cho 2-33, Minami -ku, Yokohama 232, Japan
Gan; 72(5):772-776 1981

The effects of various chemicals, such as bile acids, a lectin, polyamines, and chemical carcinogens, on metabolic cooperation in the hypoxanthine-guanine phosphoribosyl transferase system were surveyed. Among bile acids, lithocholic acid, chenodeoxycholic acid and ursodeoxycholic acid inhibited metabolic cooperation. However, cholic acid, deoxycholic acid and dehydrocholic acid did not. There was a structure-activity relationship among these compounds for the inhibition of metabolic cooperation. The metabolic cooperation was not inhibited by such chemicals as phytohemagglutinin, three polyamines, 7,12-dimethylbenz[a]anthracene, N-methyl-N'-nitro-N-nitrosoguanidine, 4-nitroquinoline 1-oxide and three biphenyl compounds. These results should be useful in relation to studies on the mechanism of inhibition of metabolic cooperation and on the relationship between this inhibitory activity and the tumor-promoting activity of various chemicals. (Author abstract) (12 Refs)

28. DNA SYNTHESIS INHIBITORS (SKIN CHALONES AND HYDROXYUREA) ENHANCE TUMOUR PRODUCTION AFTER A SINGLE APPLICATION OF METHYLNITROSOUREA TO HAIRLESS MOUSE SKIN (MEETING ABSTRACT).

Iversen OH
McArdle Laboratory for Cancer Research, Madison, WI
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. The Congress 92 pp., 1981.

Hairless mouse epidermis was treated topically with 1 mg methylnitrosourea in acetone. Three groups had been given ip pretreatment with epidermal extracts, and one group with 5 mg hydroxyurea ip 30 min before the carcinogen. Control groups were injected with muscle- or skin extract, saline or Colcemid. One control group was without pretreatment. Contrary to expectations, the groups with depressed epidermal DNA synthesis by skin chalone or hydroxyurea developed sig-

nificantly more tumors than the other groups. Hence, under the experimental conditions used, an inhibited DNA synthesis at the time of the carcinogen application significantly enhanced carcinogenesis. Various possible mechanisms are discussed. (no Refs)

29. PG SYNTHESIS AND BINDING BY GROWING AND REGRESSING RAT MAMMARY CARCINOMA (MEETING ABSTRACT).

Liu SC, Knazek RA
Laboratory of Pathophysiology, National Cancer Institute,, National Institutes of Health Bethesda, MD
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Mammary tumors induced in Buffalo rats by nitrosomethyl urea are known to regress after oophorectomy. Their ability to synthesize and bind prostaglandins E and F2alpha were studied in the growing and regressing states. The tumor was homogenized in sucrose-tris buffer and after a preliminary 120xg spin, was centrifuged at 15,000xg or 100,000xg. Either 3H-PGE2 or 3H-PGF2alpha was incubated for 45 mi n at room temperature with a suspension of the 15,000 xg pellet +/- excess unlabeled PG. Free prostaglandins were separated from those bound to the membrane by filtration through Whatman GF/C filters. Binding of both PGE2 and PGF2alpha reached equilibrium after 30 min incubation, was saturable, and was reversible. Scatchard analyses were compatible with the presence of high and low affinity binding sites. A sudden 2-3-fold increase in specific binding was observed 4 days after oophorectomy and was sustained for at least 4 additional days. Aqueous suspensions of tumor 100,000 xg membranes were incubated for 2 hr at 37C +/-5x10(-4) indomethacin, extracted into chloroform, and partially purified using silica gel column chromatography before assay by specific PG radioimmunoassay. The amount of PGE and F2alpha synthesized rose from 0.13 and 10.5 ng/mg protein in the growing tumors to a max of 1.2 and 26.5 ng/mg protein 5 days after oophorectomy. This suggests that the oophorectomy-induced increase in detectable receptor binding was not due to decreases in endogenous PG levels. The presence of PG receptors and their modulation under conditions of regression suggest a direct role of PG in the growth and regression processes of this hormone dependent mammary tumor. (no Refs)

MUTAGENICITY OF NITROSO COMPOUNDS

30. INFLUENCE OF MICROSOMAL AND CYTOSOLIC FRACTIONS FROM RAT, MOUSE, AND HAMSTER LIVER ON THE MUTAGENICITY OF DIMETHYLNITROSAMINE IN THE SALMONELLA PLATE INCORPORATION ASSAY.

Prival MJ, Mitchell VD
Genetic Toxicology Branch, Dept. Health and Human Services, Food and Drug Admin., Washington, DC, 20204
Cancer Res; 41(11,part1):4361-4367 1981

Dimethylnitrosamine (DMN) was mutagenic in the Salmonella plate incorporation assay (Ames test) at a level of 10 umol/plate (3.7 mM) in the presence of hamster liver S-9. Mutagenicity of DMN at this level was not observed when the S-9 was derived from mouse or rat liver, although the mouse liver and hamster liver S-9 had similar DMN demethylase activities. Both mouse and rat liver S-9 inhibited the mutagenicity of DMN mediated by hamster liver S-9; the inhibitory factor was contained in the microsomal fraction. Mouse or rat liver microsomes did not inhibit the DMN demethylase activity of hamster liver S-9. The microsomal inhibitor from rat or mouse liver was stable at 60 but was inactivated at 70 C. DMN demethylase from both rat and mouse liver was inactivated at 60 C. Although the DMN demethylase activity of hamster liver S-9 was contained in the microsomal fraction, DMN mutagenesis under conditions of the assay required the presence of both microsomal and cytosolic (S-105) fractions; the cytosols from hamsters, mice, and rats were all effective. The cytosolic factor required for DMN mutagenesis was sensitive to trypsin and was not dialyzable. The presence of an inhibitor of DMN activation in rat and mouse microsomes may account for, or contribute to, the failure of liver S-9 preparations from these species to activate DMN to a mutagen under standard conditions of the Ames test. The requirement for the cytosolic fraction may indicate that DMN demethylase is not sufficient for the activation of DMN to a mutagen under the conditions used in these studies. (Author abstract) (46 Refs)

31. GREATER EFFECTIVENESS OF HEPATOCYTE AND LIVER S9 PREPARATIONS FROM HAMSTERS THAN RAT PREPARATIONS IN ACTIVATING N-NITROSO COMPOUNDS TO METABOLITES MUTAGENIC TO SALMONELLA.

Raineri R, Polley JA, Andrews AW, Pienta RJ, Lijinsky W
Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, Post Office Box B, Frederick, MD, 21701
JNCI; 67(5):1117-1122 1981

A comparison was made of the ability of liver S9 and hepatocyte preparations from noninbred Syrian golden hamsters and noninbred Sprague-Dawley rats to metabolically activate a number of nitroso compounds in the Salmonella mutagenesis assay. The liver S9 and hepatocyte preparations from hamsters were consistently more effective than were preparations from rats in metabolizing nitrosodimethylamine (NDM), nitrosodiethylamine, nitrosodiallylamine, nitrosopyrrolidine (NP), nitrosomorpholine (NM), nitrosodiethylmethylurea (NDEMU), and nitrosodimethylethylurea (NDMEU) to mutagenic forms. The use of hamster S9 preparations with NP and NM resulted in up to 14x the number of revertant colonies obtained with rat preparations; in the presence of hamster hepatocytes, up to 32x the number of revertants were obtained. The S9 preparations from male hamsters not treated with the enzyme inducers phenobarbital and Aroclor 1254 were more effective than were those from female hamsters for activating NP, NM, and NDM. NDEMU and NDMEU, which have been reported to be carcinogens but not mutagens, were mutagenic in the presence of induced liver S9 or hepatocyte preparations from hamsters but not from rats. When tested with any of the S9 or hepatocyte preparations, nitrosodiphenylamine and nitrosomethylaniline, also reported to be carcinogens but not mutagens, gave no mutagenic responses. Nitrosodioctylamine, which has been reported to be noncarcinogenic, was also not mutagenic. (Author abstract) (23 Refs)

32. RADIOSTERILIZATION OF RAT LIVER MICROSOME CONTAINING POSTMITOCHONDRIAL SUPERNATANT FOR MUTATION ASSAYS.

Barfknecht TR, Andon BM, Bishop WW, Thilly WG
Genetic Toxicology Res. Group, Room E18-666, Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Environ Mutagen; 3(5):565-573 1981

Gamma-irradiation was tested as a method for sterilizing commercially prepared rat liver postmitochondrial supernatant (PMS) by adding a known number of radio-resistant Bacillus subtilis spores to PMS samples and determining a dose-response survival curve for the spores following gamma-irradiation. At the same time, uncontaminated samples of PMS were irradiated and assayed for their ability to metabolically activate automobile diesel soot (ADS) and soot-derived polycyclic aromatic hydrocarbons (PAH) and dimethylnitrosamine (DMN) to mutagens using the Salmonella typhimurium 8-azaguanine resistance forward mutation system. Based on the survival of B subtilis spores in frozen gamma-irradiated PMS, sterilization of PMS with a dose of 3 megarads (Mrad) was effective in reducing a contamination of 1,000 bacteria/ml or 10(6) bacteria/liter to 10(-3) bacteria/liter. At doses up to 6 Mrad at dose rates of 5 x 10(5) rads/hr there was little or no significant loss of the ability of irradiated PMS to metabolically activate ADS, and the diesel soot components, benzo(a)pyrene (BaP) and fluoranthene (FLA) to mutagens. At higher doses of gamma-irradiation, and at a dose rate of 3 x 10(6) rads/hr for 6 Mrad, a significant inactivation of the ability of PMS to activate BaP and FLA was noted. Thus, radiosterilized PMS can be used in mammalian cell mutation assay systems to detect PAH mutagenesis. (25 Refs)

33. ENHANCEMENT OF N-HYDROXY-2-AMINOFLUORENE BACTERIAL MUTAGENICITY BY THE SOLUBLE PROTEIN FRACTION FROM RAT LIVER AND PARTIAL PURIFICATION OF THE ENHANCEMENT ACTIVITY.

Saccone GT, DasGupta BR, Pariza MW
(c/o Pariza) Dept. Food Microbiology and Toxicology, Univ. Wisconsin, Madison, WI, 53706
Cancer Res; 41(11,part1):4600-4605 1981

Bacterial mutagenesis from 2-aminofluorene mediated by washed rat liver microsomes was elevated 2-to 3-fold by addition of the hepatic soluble protein fraction. Enhancement was observed at 2-aminofluorene concentrations between 1 and 20 ug/assay but not at 30 to 50 ug/assay. The soluble protein fraction (without added microsomes) did not activate 2-aminofluorene for bacterial mutagenesis. However, mutagenesis by N-hydroxy-2-aminofluorene or 2-nitrosofluorene was enhanced by the soluble protein fraction, but only when reduced nicotinamide adenine dinucleotide phosphate was also present. On the basis of chemical assay, reduced nicotinamide adenine dinucleotide phosphate reduced 2-nitrosofluorene to N-hydroxy-2-aminofluorene and protected the hydroxylamine from oxidation, thus indicating that it was the mutagenicity of N-hydroxy-2-aminofluorene (but not 2-nitrosofluorene) which was enhanced by the soluble protein fraction. Without the added soluble protein fraction, mutagenesis by N-hydroxy-2-aminofluorene or 2-nitrosofluorene was unaffected by reduced nicotinamide adenine dinucleotide phosphate. We succeeded in partially purifying a protein fraction with properties of the enhancement activity. The partially purified fraction, which represents a 14-fold increase in specific activity, was assigned a mol wt of 33, 500 by gel filtration through Sephadex G-100. This fraction was resolved into three components by polyacrylamide gel electrophoresis; the mol wt of the three components were determined by sodium dodecyl sulfate-polyacrylamide gel (10%) electrophoresis to be 33,000, 27,000, and 16,250. The mechanism of mutagenesis enhancement remains unknown. (Author abstract) (27 Refs)

34. STRUCTURAL BASIS OF THE MUTAGENICITY IN BACTERIA OF NITRATED NAPHTHALENE AND DERIVATIVES.

McCoy EC, Rosenkranz EJ, Petrullo LA, Rosenkranz HS, Mermelstein R
Center for Environmental Health Sciences, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH, 44106
Environ Mutagen; 3(5):499-511 1981

The mutagenic activity of nitronaphthalenes and some of their derivatives was investigated in the Salmonella mutagenicity assay. The 2-nitro and 2-hydroxylaminonaphthalenes were more mutagenic than their corresponding 1-substituted analogs. The adducts induced by 1-nitronaphthalene differed chemically from those derived from the 2-nitro analog. For expression of the mutagenic action of these chemicals, reduction of the chemicals to the corresponding hydroxylamines was required. These differences in mutagenic responses may be due to the different DNA adducts that have been identified after reaction of hydroxylaminonaphthalenes with DNA. The nitroso-containing polycyclic chemicals might not derive their mutagenic activity from reduction to the corresponding hydroxylamines. If there is a relationship between mutagenicity in Salmonella and human risks, adjusting the conditions for combustion in engines such that extensive nitration is favored may decrease the emission of hazardous substances. On a molar basis, when a mutagen is capable of inducing frameshift mutations by adduct formation as well as by simple intercalation, then the activity induced by the adduct greatly exceeds the activity due to simple intercalators. While bicyclic 2-nitronaphthalene and 4-nitroquinoline-1-oxide and their metabolites are primarily base-substitution mutagens, the introduction of a third ring structure results in a different mutational mechanism leading to frameshift mutagens. (58 Refs)

35. MUTAGENICITY OF ISOMERIC BETA, GAMMA, GAMMA-UNSATURATED N-NITROSAMINES DERIVED FROM TERPENE ALKANOLAMINES.

Abidi SL, Finch RA
P. O. Box 65, La Crosse, WI, 54601
Environ Mutagen; 3(5):587-591 1981

The Ames Salmonella/microsome mutagenicity test was performed on a 1:2 mixture of cis-N-nitroso-2(3',7'-dimethyl-2',6' octadienyl)aminoethanol (cis-NDOA) and trans-N-nitroso-2(3',7'-dimethyl-2',6' octadienyl)aminoethanol (trans-NDOA). With the cis,trans-NDOA mixture, tested at dose levels of 50, 100, and 250 ug/incubation mixture (IM), without S-9 activation, no significant increase in the number of revertant colonies/plate was seen in any of the tester strains and no dose-response relationship was noted. At doses of 500 and 100 ug/IM in the presence of S-9 activation, significantly greater numbers of revertant colonies were noted only in tester strains TA100 and TA1535. A cytotoxic effect was noted in all the tester strains at a dose level of 250 ug/IM. A slight cytotoxic effect was noted in strain TA1535 at a dose level of 100 ug/IM. It was concluded that under the conditions of the test, the mixture of cis and trans isomers of NDOA is mutagenic for the Salmonella tester strains TA100 and TA1535 in the presence of Aroclor 1254-induced rat liver S-9 activation system. (6 Refs)

36. COMPARISON OF THE MUTAGENIC ACTIVITY OF DIALKYLNITROSAMINES IN ANIMAL-MEDIATED AND IN VITRO ASSAYS USING AN ESCHERICHIA COLI INDICATOR.

Kerklaan P, Mohn G, Bouter S
Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, Leiden, The Netherlands
Carcinogenesis; 2(9):909-914 1981

The mutagenicity of six dialkylnitrosamines was tested in intrasanguineous host-mediated and in vitro assays. In the host-mediated assay, Swiss albino mice were inoculated iv with Escherichia coli cells and immediately after with test compound. Within different time periods up to 300 min after exposure the mice were sacrificed and liver and spleen homogenates were plated on selective agar media. Yield of mutations in the host-mediated assay was in better agreement with carcinogenicity data than the mutation yield obtained in vitro using induced or uninduced rat liver S-9 fractions. (23 Refs)

37. LUNG AND LIVER CELL-MEDIATED MUTAGENESIS SYSTEMS: SPECIFICITIES IN THE ACTIVATION OF CHEMICAL CARCINOGENS.

Langenbach R, Nesnow S, Tompa A, Gingell R, Kuszynski C
Carcinogenesis and Metabolism Branch (MD 68), Genetic Toxicology Div., Health Effects Res. Lab., US Environmental Protection Agency, Research Triangle Park, NC, 27711
Carcinogenesis; 2(9):851-858 1981

Carcinogens from three chemical classes were compared for mutagenicity in systems containing cocultivated adult Sprague Dawley rat hepatocytes or lung cells and Chinese hamster V79 cells. 7,12-dimethylbenz[a]anthracene (DMBA), 3-methylcholanthrene (MCA), and benzo[a]pyrene (BP) were mutagenic for V79 cells in the lung cell-mediated system. DMBA and MCA were less mutagenic in the liver system, and BP was negative in this system. Aflatoxin B1 was mutagenic in the liver cell system but was only weakly mutagenic in the lung cell system. Dimethylnitrosamine (DMN) was mutagenic only in the presence of liver cells. The metabolism of BP and DMN was investigated to gain insight into the causes of their organ specificity. For DMN, the lack of metabolic activation by rat lung cells apparently accounted for its lack of mutagenicity in the lung cell-mediated system. BP was metabolized by both systems, but quantita tive differences were observed in the metabolites detected. Lung cells produced primarily the 7,8-and 9,10-diols and little detectable 4,5-diol, whereas liver cells produced the 4,5-diol as the major metabolite. (38 Refs)

38. SOME EFFECTS OF TREATMENT OF HEN ERYTHROCYTES IN VITRO WITH N-METHYL-N-NITROSOUREA.

Ward TH, Itzhaki RF
Paterson Lab., Christie Hosp., Manchester M20 9BX, England
J Cell Sci; 51:153-162 1981

Studies have been made of the effect of N-methyl-N-nitrosourea on hen RBC in vitro. These were done to find whether the highly condensed state of the chromatin and the very low metabolic activity of these cells would affect the extent of methylation of the DNA and chromatin proteins and the persistence of any methylation sites in these macromolecules with time after treatment. Also, the effect of methylnitrosourea on incorporation of [3H]uridine into RNA has been examined. It has been found that the DNA, histones and non-histone proteins are methylated. The main methylation site in DNA is 7-methylguanine and its level is higher that that found by others in the DNA of other cell types after treatment with methylnitrosourea; however, methylation of the two types of protein (especially the histones) is relatively very low. The level of methylation decreases in the DNA and the chromatin proteins with time after treatment. The amount of [3H]uridine in RNA was found to decrease after the treatment. (Author abstract) (19 Refs)

39. HUMAN SALIVA INACTIVATES MUTAGENICITY OF CARCINOGENS.

Nishioka H, Nishi K, Kyokane K
Div. Biochemistry, Doshisha Univ., Kyoto, Japan
Mutat Res; 85(5):323-333 1981

Various carcinogens, suspected carcinogens, certain pyrolysates (beef, salmon, sodium glutamate, polypeptone), and cigarette smoke condensate (CSC) were incubated with human saliva from healthy subjects. Effects on mutagenicity were tested in a modified Ames test with Salmonella typhimurium strains TA 98 and TA 100. Metabolic activation for development of mutagenicity was required by aflatoxin B1, benzo(a)pyrene (BP), tryptophan pyrolysate-1 (Tr-P-1, isolated from boiled beef), the other pyrolysates, and CSC. No metabolic activation was required by 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2; a nitrofuran used as a food additive during 1966-1975 in Japan), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), methyl methanesulfonate (MMS), 4-nitroquinoline 1-oxide (4NQO) and quercetin. Saliva inactivated AF-2, MNNG, 4NQO, aflatoxin B1, BP, and Trp-P-1. Mutagenic activities of quercetin, pyrolysates of beef, salmon, and sodium glutamate, and CSC decreased to some extent; the activities of MMS and polypeptone pyrolysate were not affected. Boiled saliva inactivated AF-2 somewhat in TA 98 but not in TA 100 cultures. Complex mechanisms may be involved in the inactivation of mutagenicity of carcinogens by saliva. (22 Refs)

40. CHEMICAL CARCINOGENESIS IN THE RAT: COMMON MODE OF ACTION OF CARCINOGENS AT THE CHROMOSOME LEVEL.

Sugiyama T, Ueda N, Maeda S, Shiraishi N, Goto-Mimura K, Murao S, Chattopadhyay SC
Dept. Pathology, Kobe Univ. Sch. Medicine, Chuo-ku, Kobe, Japan 650
JNCI; 67(4):831-839 1981

The chromosomal distribution of chromosome aberrations (CA) and sister chromatid exchanges (SCE) induced by various chemical carcinogens such as 7,12-dimethylbenz[a]anthracene, 7,8,12-trimethylbenz[a]anthracene, 1-butyl-1-nitrosourea, urethan, 4-nitroquinoline 1-oxide, 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, and the antineoplastic compound mitomycin C was studied with the use of noninbred Long-Evans male rat bone marrow cells in vivo and in vitro. The CA and SCE induced by these structurally different chemicals were distributed in similar pattern among and along chromosomes when the chemicals were given a short time (6 hr) before the metaphase cells were harvested. The specific distribution pattern of chemically induced CA and SCE along chromosomes was attributed to the late DNA replication of the vulnerable chromosome regions. Conversely, x-ray-induced CA were distributed more randomly. Thus the different chemical carcinogens were shown to exert a similar genetic effect at the chromosome level. (Author abstract) (38 Refs)

CELLULAR EFFECTS OF NITROSO COMPOUNDS

41. 32P-LABELING TEST FOR DNA DAMAGE.

Randerath K, Reddy MV, Gupta RC
Dept. Pharmacology, Baylor Coll. Medicine, Texas Medical Center, Houston, TX, 77030
Proc Natl Acad Sci USA; 78(10):6126-6129 1981

Covalent adducts formed by the reaction of DNA with chemical carcinogens and mutagens may be detected by a 32P-labeling test. DNA preparations exposed to chemicals known to bind covalently to DNA [N-methyl-N-nitrosourea, dimethyl sulfate, formaldehyde, beta-propiolactone, propylene oxide, streptozotocin, nitrogen mustard, and 1,3-bis(2-chloroethyl)-1-nitrosourea] were digested to a mixture of deoxynucleoside 3'-monophosphates by incubation with micrococcal endonuclease (EC 3.1.31.1) and spleen exonuclease (EC 3.1.16.1). The digests were treated with [gamma-32P]ATP and T4 polynucleotide kinase (ATP:5'-dephosphopolynucleotide 5'-phosphotransferase, EC 2.7.1.78) to convert the monophosphates to 5'-32P-labeled deoxynucleoside 3',5'-bis-phosphates. These compounds were then separated on polyethyleneimine-cellulose thin layers in ammonium formate and ammonium sulfate soln. Autoradiograms of the chromatograms obtained by this high-resolution procedure showed the presence of nucleotides derived from chemically altered, as well as normal, DNA constituents. Maps from DNA exposed to any of the chemicals used exhibited a spot pattern typical for the particular chemical. This method detected a single adduct in 10(5) DNA nucleotides without requiring that the compound under investigation be radio active and thus provides a useful test to screen chemicals for their capacity to damage DNA by covalent binding. (Author abstract) (41 Refs)

42. THE FORMATION AND REPAIR OF O6-METHYLGUANINE IN RAT LIVER NUCLEOLAR DNA AFTER DIMETHYLNITROSAMINE ADMINISTRATION STUDIED BY RADIOIMMUNOASSAY.

Kyrtopoulos SA, Vrotsou B
Natl. Hellenic Res. Foundation, Biological Res. Centre, 48, Vassileos Constantinou Ave., Athens, T.T. 501/1, Greece
Chem Biol Interact; 37(1):191-197 1981

The extent of formation and the rate of O6-methylguanine repair in rat liver nucleolar DNA following administration of a single dose of dimethylnitrosamine have been studied by means of radioimmunoassay for O6-methyldeoxyguanosine. No difference has been found in either the extent of formation or the rate of repair of this lesion between nucleolar and whole nuclear DNA. (Author abstract) (36 Refs)

43. THE ORGAN CULTURE OF RAT ESOPHAGEAL MUCOSAL EPITHELIUM AND ITS RESPONSE TO N'-NITROSONORNICOTINE (MEETING ABSTRACT).

Reiss B, Hecht SS, Williams GM
Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
In Vitro; 17(3):223 1981

Using techniques similar to those beneficial for the prolonged organ culture of rodent colon, we have maintained rodent esophagus for up to 35 days. During this interval, the normal architecture and histology of the mucosal epithelium were preserved, and normal cell proliferation and keratinization were retained. Kinetic studies of cells labelled during DNA synthesis demonstrated a continuation of epithelial cell maturation and migration for at least 4 wk. Exposure to the model esophageal carcinogen, N'-nitrosonornicotine (NNN; 10(-2) M) for 48 hr in culture suppressed DNA synthesis of conventional rat esophageal mucosa at 2 days; higher incorporation than controls occurred at 1, 2 and 3 wk. Exposure to 14C-NNN for 48 hr resulted in the formation of 4-oxo-4-(3-pyridyl)butyric acid from 2'-hydroxylation and 4-hydroxy-4-(3-pyridyl)butyric acid from 5'-hydroxylation of NNN. The levels of these metabolites indicated that, unlike the hepatic metabolism of NNN, the extent of 2'-hydroxylation in the esophagus exceeds that of 5'-hydroxylation. These results may provide the metabolic basis for the organo-selectivity of NNN. Fragments of organ-cultured esophagus implanted into mammary fat pads of syngeneic animals have been maintained for up to 6 mo. Fragments exposed to NNN for 48 hr and then implanted developed a hyperplastic mucosal epithelium after 2 mo in the host. This potentially preneoplastic change was not observed in controls. (1 Ref)

44. TRANSFORMATION OF EPITHELIAL CELLS FROM CARCINOGEN-TREATED RAT ESOPHAGUS (MEETING ABSTRACT).

Stoner GD, Babcock MS
Medical College of Ohio, Toledo, OH, 43614
In Vitro; 17(3):236 1981

In this report, we describe the development of an in vitro model for the study of carcinogen induced esophageal cancer. Primary explant cultures of rat esophagus were treated with the potent esophageal carcinogen, N-nitrosomethylbenzylamine (MBN) at concentrations of 10, 5, 2.5 and 1 ug per ml on days 1 and 7 after initiation of the cultures. After incubation for 2-3 mo, epithelial cells in cultures treated with 10, 5 or 2.5 ug per ml could be subcultured and cell lines developed. Attempts to subculture epithelial cells from explants treated with either 1 ug MBN per ml or with dimethylsulfoxide (solvent control) were unsuccessful. Electron microscopy revealed that the subcultured cells contain morphological markers of epithelial cells: numerous tonofilaments and junctional complexes. By immunofluorescence, the cells reacted positively with antibodies prepared to mouse skin keratins. In early passage, the growth of the cells was stimulated by the addition of epidermal growth factor to the medium. Some of the cell lines exhibited characteristics of neoplastic cells: they are aneuploid, form colonies from single cells in soft agar, and produce squamous cell carcinomas after transplantation into syngeneic newborn rats or athymic, nude mice. (no Refs)

45. EFFECTS OF THE CARCINOGEN, N-METHYL-N'-NITRO-N-NITROSOGUANIDINE (MNNG), ON NORMAL HUMAN PROSTATE EPITHELIUM IN EXPLANT CULTURE (MEETING ABSTRACT).

Sanefuji H, Heatfield BM, Trump BF
Department of Pathology, University of Occupational and Environmental Health School of, Medicine Kitakyushu 807, Japan
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. The Congress 92 pp., 1981.

Explants of normal human prostate were cultured at 37 C in CMRL-1066 medium supplemented with fetal calf serum and antibiotics. Viable explants were maintained up to 1 yr in vitro, and basal cell derivatives were thought to be viable in explant culture. MNNG, dissolved in dimethylsulfoxide (DMSO), was added to the culture medium. Cultures without MNNG and those with DMSO alone served as controls. Explants exposed

to MNNG showed marked proliferation of atypical epithelial cells, which were histopathologically consistent with premalignant or malignant changes. That is, these cells possessed bizarre, pleomorphic and hyperchromatic nuclei with conspicuous nucleoli. Bizarre mitotic figures were occasionally seen. Some of these explants were transplanted in athymic nude mice. (no Refs)

46. EPITHELIAL FOCUS ASSAY FOR EARLY DETECTION OF CARCINOGEN-ALTERED CELLS IN VARIOUS ORGANS OF RATS EXPOSED IN SITU TO N-NITROSOHEPTAMETHYLENEIMINE.

Terzaghi M, Nettesheim P, Yarita T, Williams ML
Biology Div., OakRidge Natl. Lab., P.O. Box Y, Oak Ridge, TN, 37830
JNCI; 67(5):1057-1062 1981

The purpose of these studies was to determine (a) whether epithelial cells with altered in vitro growth capacity occur not only after topical application of 7-12-dimethylbenz[a]anthracene but also after systemic administration of a carcinogenic nitrosamine, and (b) whether such cells can be isolated from tissues other than tracheal mucosa. At 3 and 20 wk following intragastric administration of 150, 300, or 600 mg N-nitrosoheptamethyleneimine (NHMI)/kg, cells were harvested from tracheas, esophagi, and lungs (target tissues for NHMI) of inbred F344 rats and seeded into culture dishes. Normal cells from nonexposed organs produced no proliferative epithelial foci (EF). Of those tracheas sampled 3 wk following exposure to 150 and 300 mg/kg, 10 and 20%, respectively, contained one or more EF that could be subcultured. Of those tracheas harvested 3 wk post exposure to 600 mg/kg or 20 wk post exposure to 150-600 mg/kg, 80-100% contained EF that could be subcultured. Twenty wk after 600 mg NHMI/kg, the incidence of tracheas harboring cell populations with neoplastic potential (agarose-positive EF) was 80%, whereas the tracheal tumor incidence determined at 24 mo was only 29%. Epithelial focus-forming units with various abnormal in vitro growth potentials were also detected in esophagi and lungs of NHMI-exposed rats. (Author abstract) (15 Refs)

47. INDUCTION OF ORNITHINE DECARBOXYLASE IN CULTURED MAMMARY TUMOR CELLS (MEETING ABSTRACT).

Cohen LA, Van der Snoek L
Naylor Dana Institute for Disease Prevention, Valhalla, NY, 10595
In Vitro; 17(3):242 1981

At present, little is known concerning the role played by polyamines in mammary cancer. Since in vivo studies are difficult to interpret at the cellular level, we have developed a defined in vitro system consisting of neoplastic epithelial cells derived from an N-nitrosomethylurea induced rat mammary adenocarcinoma. Ornithine decarboxylase (ODC), the rate-limiting step in polyamine synthesis, was measured in these cells by the in situ method of Patterson and Maxwell. To induce ODC, late log-phase cells were grown in serum-depleted medium. The kinetics of ODC induction was similar to that reported in other cell lines. Specific activity (sp act) at 0, 15 and 60 min was less than 0.5, 3.25 and 6.30 nmoles carbon dioxide/mg prot/hr, respectively; between 1 and 2 hr little change in sp act was observed. The specificity of the reaction was assessed by addition of inhibitors of the reaction mixture for the 2 hr assay period. There was an absolute requirement for pyridoxal phosphate; the reaction product, putrescine, inhibited ODC in a logarithmic fashion, and the competitive inhibitor alpha-methylornithine reduced enzyme activity by half. (1 Ref)

48. INITIATION OF C3H/10T1/2 TRANSFORMATION BY DIRECT-ACTING ALKYLATING AGENTS (MEETING ABSTRACT).

Boreiko CJ, Frazelle JH, Abernethy DJ, Ragan DL
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
In Vitro; 17(3):201 1981

C3H10T1/2 Cl 8 mouse embryo fibroblasts can be oncogenically transformed by numerous carcinogens, but are reported to be relatively insensitive to the oncogenic potential of simple alkylating agents such as N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). This lack of sensitivity is surprising in view of reports that MNNG is mutagenic for these cells. Since C3H/10T1/2 transformation can be demonstrated to progress through the discrete stages of initiation and promotion, we have examined the ability of alkylating agents to act as initiating agents. MNNG (0.1-0.5 ug/ml) and formaldehyde (0.1-2.5 ug/ml) produced transformed foci in a dose dependent fashion if carcinogen treatment with 0.1 ug/ml of the tumor promoter 12-O-tetradecanoyl phorbol-13-acetate (TPA). Foci were produced in 19 of 65 dishes treated with 1 ug/ml formaldehyde + TPA, and in 24 of 62 dishes treated with 0.5 ug/ml MNNG + TPA. Foci were rarely observed in solvent treated controls or MNNG treated dishes not treated with TPA. Phorbol did not promote focus production by MNNG. In contrast, TPA inhibited focus production by 1 ug/ml concentrations of the transforming agent 3-methylcholanthrene. These findings suggest that, when used for the detection of carcinogens, the C3H/10T1/2 transformation bioassay should be conducted in the presence and absence of appropriate tumor promoters. (no Refs)

49. SERUM-FREE GROWTH OF CHEF/18 AND MUTANT CELL LINES (MEETING ABSTRACT).

Sager R, Bennett F, Smith BL
Sidney Farber Cancer Institute, Boston, MA
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

The growth factor requirements of non-tumorigenic cells grown for many passages in SF medium, and of transformed mutants and cell hybrids are correlated with their tumor forming ability. CHEF/18 cells maintain a growth rate indistinguishable from that in 10% serum (FBS) when grown for many passages in SF medium. However, cells round up and form tight balls resembling foci above the monolayer. Cells derived from foci do not clone in methylcellulose (MC) nor make tumors in nude mice. The foci arising in SF-medium do not form when thrombin or epidermal growth factor (EGF) is omitted from the medium, suggesting that either factor can induce similar reversible cytoskeletal and surface changes. Growth factor requirements were examined in a series of anchorage-independent (anch) and low serum (LS) mutants derived from CHEF/18 after mutagenesis with ethyl methane sulfonate or N-methyl-N'-nitro-N-nitrosoganidine. The anch mutants require the same growth factors in SF-medium as the CHEF/18 parent. Although they clone well in MC medium + 10% serum, the anch mutants do not grow at all in SF MC medium. Similarly, the spontaneous low serum and anchorage-independent mutant CHEF/16, which is tumorigenic, and grows in SF medium does not clone in SF MC medium. Thus, the added growth factors lack some serum component required for anchorage free growth. Of the 12 mutants studied, 4 have a reduced insulin requirement. None of them have lost their EGF or thrombin requirements for SF growth and none have

become tumorigenic. The correlation between loss of the EGF requirement and gain of tumor forming ability, previously proposed by Cherington et al is confirmed by the behavior of these mutants. Further confirmation of this correlation come from studies of cell hybrids formed by fusions between non-tumorigenic mutants derived from CHEF/18 and tumorigenic derivatives of CHEF/16. (no Refs)

50. DIFFERENTIAL RESPONSE OF ELUTRIATED 9L CELLS TO TREATMENT WITH 1,3-BIS(2-CHLOROETHYL)-1-NITROSOUREA.

Hoshino T, Deen DF, Williams ME, Sano Y
Brain Tumor Res. Center, Dept. Neurological Surgery, Sch. Medicine, Univ. California, San Francisco, CA, 94143
Cancer Res; 41(11,part1):4404-4407 1981

Earlier cytokinetic studies using 9L monolayer culture cells showed that cells began accumulating in the G2 phase (4C position in the DNA distribution) within 30 hr after administration of 1,3-bis(2-chloroethyl)-1-nitrosourea (3 ug/ml). Most of these cells reached the G2 phase at 48 hr and remained there for another 24 hr. Similar studies using 9L spheroid culture cells show that 9L cells also began to accumulate at the 4C DNA position 30 hr after administration of 1,3-bis(2-chloroethyl)-1-nitrosourea (3 ug/ml); however, only one-half of the cells accumulated in the 4C peak during the first 48 hr after treatment, while the other half remained at the 2C position. Those that remained at the 2C peak might correspond to the G0 cells that exist in 9L spheroids. When one-half the cells were in 2C and one-half were in 4C, the spheroids were dissociated using an enzyme cocktail and sorted using centrifugal elutriation. Cells from each elutriated fraction were analyzed for DNA content using flow cytometry and for viability using a colony-forming efficiency assay. Results indicated that in spheroids, 1,3-bis(2-chloroethyl)-1-nitrosourea (3 ug/ml) is more effective against noncycling cells and that repopulation is more vigorous in G2-arrested cells, which presumably were cycling at the time of treatment. (Author abstract) (24 Refs)

51. HYPERSENSITIVITY TO N-METHYL-N'-NITRO-N-NITROSOGUANIDINE IN FIBROBLASTS FROM PATIENTS WITH HUNTINGTON DISEASE, FAMILIAL DYSAUTONOMIA, AND OTHER PRIMARY NEURONAL DEGENERATIONS.

Scudiero DA, Meyer SA, Clatterbuck BE, Tarone RE, Robbins JH
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Proc Natl Acad Sci USA; 78(10):6451-6455 1981

Cells from patients with ataxia telangiectasia, a rare autosomal recessive disea se characterized by primary neuronal degeneration, are abnormally sensitive to the DNA-damaging chemical N-methyl-N'-nitro-N-nitrosoguanidine. We have conducted experiments to determine whether more common primary neuronal degenerations also have a hypersensitivity to this radiomimetic chemical. Fibroblast strains from 13 control donors and from 13 patients with inherited primary neuronal degenerations were treated in vitro with the chemical, and the strains' sensitivity to the chemical was then determined by measuring their ability to divide and form colonies. Twelve of the 13 patient strains, including the 6 Huntington disease and the 4 familial dysautonomia strains, were abnormally sensitive. This hypersensitivity, which is believed to reflect defective repair of the chemically-induced DNA damage, might provide the basis for presymptomatic and prenatal diagnostic tests for these disorders and for elucidating their pathogenesis. (Author abstract) (26 Refs)

TRANSPLACENTAL EFFECTS OF NITROSO COMPOUNDS

52. INCREASED CANCER INCIDENCE IN THE PROGENY OF MALE RATS EXPOSED TO ETHYLNITROSOUREA BEFORE MATING.

Tomatis L, Cabral JR, Likhachev AJ, Ponomarkov V
International Agency Res. Cancer, 150 cours Albert Thomas, F-69372 Lyon Cedex 2, France
Int J Cancer; 28(4):475-478 1981

Results from previous experiments have indicated the persistence of an increased cancer risk in subsequent generations following prenatal exposure to a chemical carcinogen. In the present experiment, the possible role of prezygotic events in determining cancer risk was investigated in the progeny of male rats treated with ethylnitrosourea (ENU) before mating with untreated females. Eight BDVI male rats were given a single ip dose of 80 mg/kg bw ENU and each rat was then caged at wk 1, 2, 3 and 4 after treatment with three untreated females. Fertility was lower and preweaning mortality higher in the experimental group, as compared to controls, particularly at the 4th-wk mating. Survival rates after weaning were similar in the progeny of treated males and controls, as was the total incidence of tumors. However, analysis of tumor incidence at the various organ sites showed an increased incidence of neurogenic tumors in the progeny of ENU-treated males, as compared to that of controls. (Author abstract) (28 Refs)

EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS

53. CARCINOGENESIS OF GASTRIC CANCER WITH SPECIAL REFERENCE TO ETIOLOGICAL ASPECTS.

Schmahl D
Deutsches Krebsforschungszentrum, Postfach 101 949, D-6900 Heidelberg 1, W. Germany
Zentralbl Chir; 106(15):997-1004 1981

The article discusses possible etiological factors for the carcinogenesis of stomach tumors. Apart from genetic factors, stomach carcinogenesis may be attributed to the exposure of the stomach to carcinogenic substances taken in with the food, such as pyrolysis products of certain amino acids, N-nitroso compounds or disturbances of the physiological function of the stomach, for example pathological reflux after stomach operations. The frequency of stomach cancer could not be related to occupational exposure. Geographic pathology has shown that people coming from high risk areas (eg Japan) adapt to the risk pattern of the host country when they emigrate (eg to the United States, where there is only a low risk for stomach cancer). Therefore, it is assumed that several factors play a role in the etiology of stomach cancer. (Author abstract) (16 Refs) (In GER)

54. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.

Nordberg GF, Andersen O
Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
Environ Health Perspect; 40:65-81 1981

The roles of metals in enhancing or inhibiting carcinogenesis are reviewed. Conclusive evidence of the carcinogenicity of arsenic has not yet been found, although some studies suggest it. Arsenic may act as a cocarcinogen. Selenium seems to be weakly mutagenic in bacteria and some mammalian cell cultures. Antitumor properties have been reported in experimental animals. Zinc is necessary as a trace element in the diet and may have anticarcinogenic effects. Nickel is strongly carcinogenic in experimental animals and humans. Its effects may be counteracted by manganese. Lead has not been confirmed as a carcinogen, but its presence in the environment warrants high priority research particularly on its effects in combination with other compounds. Chromium has been related to lung, and possibly stomach, cancer in man. Cadmium contributes to prostatic cancer and Leydig cell tumors. These effects can apparently be counteracted by zinc treatments. Carcinogenesis by benzo[a]pyrene, nitrosamines, and asbestos appear to be promoted by some metallic dusts. Further studies in vitro and in appropriate animal systems are urged. (155 Refs)

55. CANCER PREVENTION - PRINCIPLES AND PROBLEMS.

Schramm T
Zentralinstitut fur Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 80, 1115 Berlin-Buch, E. Germany
Z Aerztl Fortbild (Jena); 75(11/12):526-529 1981

The general principles, approaches and problems in primary cancer prevention are discussed. The majority of all cancers in humans are caused directly or indirectly by exogenous factors. The major causes of cancer include tobacco, alcohol, sunlight, industrial chemicals, radiation, drugs, and possible factors determined by the life style. The existence of threshold doses for carcinogenic factors has not yet been clarified. The individual cancer risk is determined by the interplay of such processes as carcinogenesis, cocarcinogenesis, syncarcinogenesis, and anticarcinogenesis. The possibility of nitrosation of 61 drugs available in East Germany was investigated: slight nitrosation of ethambutol, piperazine, aminophenazone Analgin, desipramine, imipramine, clomipramine, ampicillin, oxacillin, and phenoxymethylpenicillin was determined. It was possible to inhibit but not completely suppress the nitrosation of these drugs by the addition of ascorbic acid. (22 Refs) (In GER)

56. CARCINOGENIC TOBACCO-SPECIFIC N-NITROSAMINES IN SNUFF AND IN THE SALIVA OF SNUFF DIPPERS.

Hoffmann D, Adams JD
Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Cancer Res; 41(11,part1):4305-4308 1981

Human data indicate an increased risk for cancer of the oral cavity for snuff dippers. Popular snuff products from the United States, Germany, Sweden, and Denmark were analyzed for tobacco-specific N-nitrosamines (TSNA). These compounds are formed during tobacco processing from nicotine, nornicotine, and anatabine and represent the only known carcinogens in snuff. N'-Nitrosonornicotine, a moderately active carcinogen, ranged in dry snuff from 3.5 to 77 ppm; 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a relatively strong carcinogen, ranged from 0.6 to 7.0 ppm; and N'-nitrosoanatabine, thus far not bioassayed, ranged from 0.8 to 44 ppm. The concentrations of TSNA in a given snuff product can vary widely, and aging in the open air can lead to an increase in TSNA. Analysis of the saliva of snuff dippers revealed that these nitrosamines are extracted from the tobacco plug during snuff dipping and that their concentrations in saliva can vary widely between users. Efforts should be made to reduce the TSNA in snuff by modifications of the production process and by wrapping individual snuff portions in airtight packets. (Author abstract) (29 Refs)

REVIEWS INCLUDING NITROSO COMPOUNDS

57. NEW NAMES FOR TWO MAIN GROUPS OF KIDNEY TUMOURS: NEPHROTHELIAL TUMOURS AND NEPHROBLASTEMAL TUMOURS (MEETING ABSTRACT).

Yuryavichus BL
Department of Pathological Anatomy, Vilnius State University, Vilnius, Lithuanian SSR, USSR
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. The Congress 92 pp., 1981.

On the basis of histopathological, histochemical and electron microscopic studies on more than 500 tumors of the kidney in both adults and children and experimental investigations which include induction of renal tumors in rats by dimethylnitrosamine, new nomenclature is proposed for tumors of the kidney. Hypernephromas or Grawits tumors should be called 'nephrothelial tumors' and divided into two parts: 'adenoma of the kidney' and 'cancer of the kidney'. The group which is well known as Wilms' tumors or nephroblastomas should be called 'nephroblastemal tumors'. (no Refs)

U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/112

AUTHOR INDEX WITH CITATION NUMBERS

Abernethy DJ 48
Abidi SL 35
Adams JD 56
Andersen O 54
Andon BM 32
Andrews AW 31
Archer MC 3
Arffmann EJ 24
Babcock MS 44
Barfknecht TR 32
Becker FF 18
Bennett F 49
Bishop WW 32
Boreiko CJ 48
Bouter S 36
Cabral JR 52
Castro JA 20
Chattopadhyay S 40
Chen CB 6
Clatterbuck BE 51
Cohen LA 47
DasGupta BR 33
De Fenos OM 20
De Ferreyra EC 20
DeCosse JJ 19
Deen DF 50
Deschner EE 19
Diaz Gomez MI 20
Eismann C 21
Finch RA 35
Floyd RA 1
Frazelle JH 48
Furihata C 11
Gingell R 37
Godoy HM 20
Goto-Mimura K 40
Grandjean CJ 4
Gupta RC 41
Haag M 15
Hampton MJ 1
Hansen FN 24
Heatfield BM 45
Hecht SS 43
Hecht SS 6
Helgeson AS 4
Herbst C 21
Hodgson RM 14
Hoffmann D 56
Hoshino T 50
Itzhaki RF 38
Iversen OH 28
Iwaguchi T 26
Kaufman DG 22
Kaufmann WK 22
Kerklaan P 36
Khudolei VV 17
Kidwell WR 13
Kitagawa H 26
Kiuchi Y 26
Kleihues P 14
Kloppel G 7
Knazek RA 29
Kodama K 11
Koepke SR 2
Kroeger-Koepke 2
Kurman CC 8
Kurzepa H 16
Kuszynski C 37
Kyokane K 39
Kyrtopoulos SA 42
Langenbach R 37
Lawson TA 4
Leung KH 3
Lewko WM 13
Lijinsky W 31
Likhachev AJ 52
Lin D 6
Liu SC 29
Liwnicz BH 16
Loper JC 16
Luckert PH 25
Maeda S 40
Magee PN 2
Marzl A 20
Matsushima T 11
McClusky GA 2
McCoy EC 34
Medline A 23
Mendel J 21
Mermelstein R 34
Meyer SA 51
Michejda CJ 2
Mitchell VD 30
Miyakawa M 12
Mochizuki M 5
Mohn G 36
Murao S 40
Nagel D 4
Nakamura M 26
Nesnow S 37
Nettesheim P 46
Nishi K 39
Nishioka H 39
Noda K 27
Nordberg GF 54
Numoto S 10
Okada M 5
Okamura T 19
Ono T 27
Otsuka H 10
Pariza MW 33
Petrullo LA 34
Pienta RJ 31
Pollard M 25
Polley JA 31
Ponomarkov V 52
Pour PM 9
Pracht B 7
Prival MJ 30
Ragan DL 48
Raineri R 31
Randerath K 41
Rasmussen KS 24
Reddy MV 41
Reiss B 43
Rice JM 22
Robbins JH 51
Rosenkranz EJ 34
Rosenkranz HS 34
Ruckert K 7
Saccone GT 33
Sager R 49
Salmon RJ 19
Sanefuji H 45
Sano Y 50
Schmahl D 53
Schramm T 55
Scudiero DA 51
Sherlock P 19
Shiraishi N 40
Sindelar WF 8
Smith BL 49
Soukup S 15
Stoner GD 44
Strum JM 13
Sugiyama T 40
Sumi Y 12
Suzuki E 5
Tarone RE 51
Terzaghi M 46
Thilly WG 32
Thust R 21
Tomatis L 52
Tompa A 37
Trump BF 45
Ueda N 40
Umeda M 27
Van der Snoek L 47
Veit C 14
Vrotsou B 42
Wallcave L 4
Wanless IR 23
Ward TH 38
Warzok R 21
Wenk ML 22
Wiessler M 14
Williams GM 43
Williams ME 50
Williams ML 46
Wong PK 1
Yarita T 46
Yoshida M 10
Yuryavichus BL 57

CANCER INFORMATION? CANCERLINE·CANCERLINE·CANCERLINE·

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. CHEMICAL COMPOUNDS AND CANCER RISK.
Schramm T, Janisch W
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):561-565 1981
In GER

2. THE CARCINOGENICITY OF ARSENIC.
Pershagen G
Dept. Environmental Hygeine, Karolinska Inst., Stockholm, Sweden
Environ Health Perspect; 40:93-100 1981

3. THE CARCINOGENICITY OF CHROMIUM.
Norseth T
Inst. Occupational Health, Gydas vei 8, Oslo 3, Norway
Environ Health Perspect; 40:121-130 1981

4. ROLE OF COBALT, IRON, LEAD, MANGANESE, MERCURY, PLATINUM, SELENIUM, AND TITANIUM IN CARCINOGENESIS.
Kazantzis G
TUC Centenary Inst. Occupational Health, London Sch. Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, England
Environ Health Perspect; 40:143-161 1981

5. RECENT RESEARCH ON NICKEL CARCINOGENESIS.
Sunderman FW
Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
Environ Health Perspect; 40:131-141 1981

6. ROLE OF CADMIUM IN CARCINOGENESIS WITH SPECIAL REFERENCE TO CANCER OF THE PROSTATE.
Piscator M
Dept. Environmental Hygiene, Karolinska Inst., S-104 01 Stockholm, Sweden
Environ Health Perspect; 40:107-120 1981

7. CHELATING AGENTS IN BIOLOGICAL SYSTEMS.
Schubert J
Dept. Chemistry, Univ. Maryland Baltimore County, Catonsville, MD, 21228
Environ Health Perspect; 40:227-232 1981

8. BENZENE AS A RISK FACTOR.
Stobbe H
Universitatsklinik fur Innere Medizin 'Theodor Brugsch', Bereich Medizin der Humboldt-Universitat, Schumannstrasse 20/21, DDR-1040 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):575-578 1981
In GER

9. FORMALDEHYDE IN DENTISTRY: A REVIEW OF MUTAGENIC AND CARCINOGENIC POTENTIAL.
Lewis BB, Chestner SB
800-A Fifth Ave., Suite 503, New York, NY, 10021
J Am Dent Assoc; 103(3):429-434 1981

10. CARCINOGENICITY OF HYDANTOINS: DATA, HYPOTHESES, AND PUBLIC REVIEWS.
Scoville B, White BG
Natl. Inst. Neurological and Communicative Disorders and Stroke, NIH, Bethesda, MD, 20205
Psychopharmacol Bull; 17(3):195-197 1981

11. PHENOXY ACIDS, CHLOROPHENOLS, AND CANCER.
Hardell L, Eriksson M
Onkologiska kliniken, Regionsjukhuset, Umea, Sweden
Lakartidningen; 78(34):2862-2863 1981
In SWE

12. PHENOXY ACIDS: A BRIEF REVIEW OF THE POSSIBLE HYGIENIC EFFECTS.
Edling C
Yrkesmedicinska kliniken, Regionsjukhuset, Linkoping, Sweden
Lakartidningen; 78(34):2861-2862 1981
In SWE

DIETARY FACTORS IN CARCINOGENESIS

13. NUTRITIONAL MODULATION OF CANCER.
Nauss KM, Newberne PM
Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Cancer Detect Prev; 3(2):367-417 1981

14. FIBER CARCINOGENESIS: EPIDEMIOLOGIC OBSERVATIONS AND THE STANTON HYPOTHESIS.
Harington JS
Cancer Res. Dept., Natl. Cancer Assoc. South Africa, P.O. Box 2000, Johannesburg 2000, South Africa
JNCI; 67(5):977-989 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

15. EPIDEMIOLOGY.
Alderson MR
Dept. Epidemiology, Inst. Cancer Res., London, England
Recent Results Cancer Res; 78:1-19 1981

16. ATLAS OF CANCER MORTALITY IN THE PEOPLE'S REPUBLIC OF CHINA. AN AID FOR CANCER CONTROL AND RESEARCH.
Li JY, Liu BQ, Li GY, Chen ZJ, Sun XD, Rong SD
Dept. Cancer Epidemiology, Cancer Inst. Chinese Acad. Medical Sciences, 2, Yabao Lu, Chaoyang, Qu, Beijing, People's Republic of China
Int J Epidemiol; 10(2):127-133 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

17. SIXTH EAST GERMAN CANCER CONGRESS WITH INTERNATIONAL PARTICIPATION, BERLIN, MARCH 2-5, 1981.
Schramm T, Ebeling K, Schwarz R, Heise E, Glaser A, Tanneberger St, Anger G
No affiliation given
Arch Geschwulstforsch; 51(7):551-560 1981
In GER

18. EPIDEMIOLOGICAL STUDIES INTO THE POSSIBLE CARCINOGENICITY OF HAIR DYES.
Clemmesen J
(c/o P. Lohman), Medical Biological Lab. TNO., P.O. Box 45, 2280 AA Rijswijk, Th e Netherlands
Mutat Res; 87(1):65-79 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

19. THE ROLE OF METALS IN CARCINOGENESIS: BIOCHEMISTRY AND METABOLISM.
Jennette KW
Dept. Chemistry, Dartmouth Coll., Hanover, NH, 03755
Environ Health Perspect; 40:233-252 1981

20. RECENT CONCEPTS OF INITIATION AND PROMOTION IN CARCINOGENESIS.
Becker FF
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Am J Pathol; 105(1):3-9 1981

21. ACTIVATED METABOLITES OF CARCINOGENIC HYDROCARBONS.
Harvey RG
Ben May Lab., Univ. Chicago, Chicago, IL, 60637
Acc Chem Res; 14(7):218-226 1981

22. RELATIONSHIP BETWEEN METAL TOXICITY TO SUBCELLULAR SYSTEMS AND THE CARCINOGENIC RESPONSE.
Squibb KS, Fowler BA
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Environ Health Perspect; 40:181-188 1981

23. ENZYMES INVOLVED IN THE REPAIR OF DAMAGED DNA.
Grossman L
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 N. Wolfe St., Baltimore, MD, 21205
Arch Biochem Biophys; 211(2):511-522 1981

24. METAL-INDUCED INFIDELITY OF DNA SYNTHESIS.
Zakour RA, Kunkel TA, Loeb LA
Joseph Gottstein Memorial Cancer Res. Lab., Dept. Pathol., Univ. Washington, Seattle, WA, 98195
Environ Health Perspect; 40:197-205 1981

25. CHROMOSOME ABERRATIONS AND THEIR RELEVANCE TO METAL CARCINOGENESIS.
Vainio H, Sorsa M
Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Environ Health Perspect; 40:173-180 1981

MODIFICATION OF CARCINOGENESIS

26. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.
Nordberg GF, Andersen O
Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
Environ Health Perspect; 40:65-81 1981

27. EFFECT OF METALS ON MUTAGENESIS AND DNA REPAIR.
Rossman TG
Inst. Environmental Medicine, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Environ Health Perspect; 40:189-195 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

28. SISTER CHROMATID EXCHANGES: A REPORT OF THE GENE-TOX PROGRAM.
Latt SA, Allen J, Bloom SE, Carrano A, Falke E, Kram D, Schneider E, Schreck R, Tice R, Whitfield B, Wolff S
Harvard Medical Sch., Boston, MA, 02115
Mutat Res; 87(1):17-62 1981

29. EFFECTS OF METALS IN IN VITRO BIOASSAYS.
Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Environ Health Perspect; 40:163-172 1981

NOW

Your Complimentary Copy of

The Latest DIRECTORY OF CANCER RESEARCH INFORMATION RESOURCES

Just Return the Form at the Bottom of this Page

This Directory is Your Guide to the Following Information Sources:

COMPUTERIZED CANCER INFORMATION available through biomedical libraries

PRIMARY JOURNALS containing cancer-related articles

SECONDARY PUBLICATIONS such as abstract bulletins, indexes, bibliographies, etc.

INFORMATION ON PROJECT DESCRIPTIONS AND FUNDING SOURCES

ORGANIZATIONS that provide fellowships, grants, and other support of cancer research, as well as organizations that conduct research

REGISTRIES of cancer patient data

LIBRARIES with special collections of cancer-related literature

CLASSIFICATIONS used to categorize and index cancer information

SPECIAL COLLECTIONS of cancer-related materials

AUDIOVISUAL MATERIALS dealing with cancer

Request for **COMPLIMENTARY DIRECTORY:**
(*Print Clearly* for use as mailing label)

Name: _____

Address: _____

_____

City/State/Zip: _____

Country: _____

Mail to:
Directory Request
ICRDB Program
National Cancer Institute
Westwood Building Room 10A18
Bethesda, Maryland 20205

The Latest International Compilation

PHASE II / PHASE III CLINICAL TRIALS

IN CASE YOU MISSED IT, THE 1981 COMPILATION OF CANCER THERAPY PROTOCOLS IS NOW AVAILABLE

Clinical oncologists are probably familiar with the annual

Compilation of Cancer Therapy Protocol Summaries

This volume summarizes clinical trials of:

- new agents
- new techniques
- new combinations of modalities and agents

The Compilation includes nearly 1,500 Phase II and Phase III trials currently in progress in countries around the world. This information is compiled by the International Cancer Research Data Bank--a program of the National Cancer Institute. It is available to you, without charge, as a public service of the program.

FOR A COMPLIMENTARY COPY, WRITE:

(*Print Clearly* for use as mailing label)

Name: _____

Address: _____

_____

City/State/Zip: _____

Country: _____

Mail to:

Compilation Request
ICRDB Program
National Cancer Institute
Westwood Building Room 10A18
Bethesda, Maryland 20205

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
5285 Port Royal Road
Springfield, Va. 22161

OFFICIAL BUSINESS

Penalty for Private Use, $300

PRINTED MATTER

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF COMMERCE
COM-211

THIRD CLASS
BULK RATE

U.S.MAIL

CK-01

NOTICE OF MAILING CHANGE

☐ Check here if you wish to discontinue receiving this publication.

☐ Check here if your address has changed and you wish to continue receiving this publication. (Be sure to furnish your complete address including zip code.)

Tear off cover with address label still affixed and send to:

Computer Support Center
ICRDB Program
IIT Research Institute
10 West 35th Street
Chicago IL. 60616

CANCERGRAMS are distributed for the International Cancer Research Data Bank (ICRDB) by the National Technical Information Service (NTIS). CANCERGRAMS are available from NTIS on a standing order basis at $2 each for North American Continent addressees and $3 each for other addressees. An NTIS deposit account is required. For a list of subject categories or other information, please write to:

Subscription Section
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161

CK 01/82/04

NCI/ICRDB/CK01 82/04

PB82-935104

ICRDB CANCERGRAM

CHEMICAL CARCINOGENESIS

Nitroso Compounds

SERIES CK01 No. 82/04

APRIL, 1982

This Cancergram is a service of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM of the U.S. National Cancer Institute. Every few weeks, an updated Cancergram containing abstracts of selected cancer-related articles recently published in more than 3000 journals, and dealing with the topic indicated by the above title, is sent to researchers working in this area. These researchers are identified on the basis of the description of their current research project that has been submitted to the ICRDB Program, directly or via granting agencies.

This Cancergram is prepared by the Cancer Information Dissemination and Analysis Center (CIDAC) for Carcinogenesis Information. ***If this Cancergram is useful and valuable, please send your comments to the CIDAC address below, since future editions depend on user satisfaction and user needs:***

CIDAC FOR CARCINOGENESIS INFORMATION
SCIENCE INFORMATION SERVICES
FRANKLIN INSTITUTE RESEARCH LABORATORIES
20TH AND RACE STREETS
PHILADELPHIA, PA 19103

NEWARK PUBLIC LIBRARY

APR 29 1982

U. S. GOVT. PUBS.
DEPOSITORY 376

AVAILABLE: DIRECTORY OF CANCER RESEARCH INFORMATION RESOURCES, 1981 EDITION. FOR A COMPLIMENTARY COPY, CONTACT ICRDB PROGRAM, WESTWOOD BLDG., RM. 10A18, BETHESDA, MD. 20205

In this issue:

- FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS..... 1
- METABOLISM OF NITROSO COMPOUNDS..... 2-12
- INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS..... 13-43
- MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS..... 44-67
- MUTAGENICITY OF NITROSO COMPOUNDS..... 68-84
- CELLULAR EFFECTS OF NITROSO COMPOUNDS..... 85-95
- TRANSPLACENTAL EFFECTS OF NITROSO COMPOUNDS..... 96-97
- IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS... 98-100
- EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS..... 101-105
- REVIEWS INCLUDING NITROSO COMPOUNDS..... 106-114

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20.3173/2:

FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS

1. PHOTOINDUCED REACTION OF DIMETHYLNITROSAMINE WITH DNA AND POLYNUCLEOTIDES.

Arfellini G, Prodi G, Rocchi P, Grilli S
Centro di Cancerogenesi Chimica, Istituto di Canerologia, Universita degli Studi di Bologna, via S. Giacomo 14, 40126 Bologna, Italy
Photochem Photobiol; 34(5):645-648 1981

Products from dimethylnitrosamine (DMN) photolysis were found to bind with DNA a nd with synthetic polynucleotides, and some of the interaction compounds were identified. When DNA or polynucleotides were incubated with 14C-DMN and simultaneously subjected to UV irradiation at 334 nanometer covalent binding to DNA increased with time. Binding with polyguanylic acid poly(G) was 36-fold higher than that with other polynucleotides. These interactions occurred only if nucleic acids were present during DMN photolysis. Trimethylamine was the interaction product recovered in alkaline hydrolysates of polyadenylic acid, polyuridylic acid, polycytidylic acid and poly and poly(A) following the photoinduced reaction with labeled DMN. Both trimethylamine and N-methylhydrazine were recovered after the reaction of DMN with DNA and with poly(G). This physicochemical system could serve as a model of chemical carcinogenesis. (31 Refs)

METABOLISM OF NITROSO COMPOUNDS

2. COMPARATIVE METABOLISM OF 2,6-DIMETHYLNITROSOMORPHOLINE IN RATS, HAMSTERS, AND GUINEA PIGS.

Underwood B, Lijinsky W
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 42(1):54-58 1982

The metabolism of N-[3,5-3H]nitroso-2,6-dimethylmorpholine (NDMM) was studied in female Sprague-Dawley rats, Syrian golden hamsters, and guinea pigs. NDMM induces tumors in the esophagus in rats, pancreatic cancer in hamsters, and hemangioendothelial tumors of the liver in guinea pigs. An intragastric dose of NDMM (2 mg, 2 uCi/animal) was rapidly distributed throughout the tissues of both the rat and hamster, with no apparent accumulation of radioactivity in any one tissue. At low dose levels, NDMM was metabolized rapidly by both species. The hamster appeared to metabolize the compound faster than did the rat or guinea pig. An appreciable amount of radioactivity was excreted in the urine in all three species after 8 hr: approx 54% in the hamster; 39% in the rat; and 30% in the guinea pig. During the first 24 hr, only a small percentage of the radioactivity excreted by the hamster, rat, and guinea pig was NDMM (0.8, 2, and 0.5% respectively). High-pressure liquid chromatography analysis of urine collected 24 hr after administration revealed 12 metabolites. Although the urinary metabolites appeared to be similar in all three species, one large difference was the presence of a major urinary metabolite in hamster urine, which was absent or present in only small quantities in the rat and guinea pig. The guinea pig urine also had relatively more radioactivity present in one major fraction than did the hamster or rat. (Author abstract) (22 Refs)

3. METABOLIC ALPHA-HYDROXYLATION OF N-NITROSOMORPHOLINE AND 3,3,5,5-TETRADEUTERO-N-NITROSOMORPHOLINE IN THE F344 RAT.

Hecht SS, Young R
Div. Chemical Carcinogenesis, American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Cancer Res; 41(12):5039-5043 1981

We studied the metabolism in the male F344 rat of N-nitrosomorpholine and of 3,3,5,5-tetradeutero-N-nitrosomorpholine; the latter is less carcinogenic and less mutagenic than is N-nitrosomorpholine. Alpha-Hydroxylation (3-or 5-hydroxylation) of N-nitrosomorpholine by liver microsomes and a reduced nicotinamide adenine dinucleotide phosphate-generating system produced (2-hydroxyethoxy)acetaldehyde, which was identified as its 2,4-dinitrophenylhydrazone derivative. When we administered N-nitrosomorpholine to rats ip, we did not detect (2-hydroxyethyl)acetaldehyde in the urine, but we did identify (2-hydroxyethoxy)acetic acid (16% of the dose). We also identified N-nitroso(2-hydroxyethyl)glycine (33% of the dose) from beta-hydroxylation (2-or 6-hydroxylation), N-nitroso-diethanolamine (12%), and unchanged N-nitrosomorpholine (1.5%) in the urine. The deuterated analogs of the above metabolites were isolated from the urine of rats treated with 3,3,5,5-tetradeutero-N-nitrosomorpholine in yields as follows: (2-hydroxyethoxy)acetic acid (3.4%); N-nitroso(2-hydroxyethyl)glycine (37%); N-nitrosodiethanolamine (12%); N-nitrosomorpholine (0.4%). These data demonstrate that deuterium substitution in the alpha-positions of N-nitrosomorpholine caused a decrease in the extent of alpha-hydroxylation and indicate that alpha-hydroxylation is the mechanism of activation of N-nitrosomorpholine. (Author abstract) (31 Refs)

4. METABOLIC ALPHA-HYDROXYLATION OF N-NITROSOMORPHOLINE (MEETING ABSTRACT).

Hecht SS, Young R, Chen CB
American Health Foundation, Valhalla, NY, 10595
Toxicologist; 1(1):35 1981

N-Nitrosomorpholine (NM) is a potent carcinogen which induces liver tumors in rats and tumors of the trachea and nasal cavity in Syrian golden hamsters. 3,3,5,5-TetradeuteroNM is less carcinogenic and less mutagenic than NM, indicating that the metabolic activation of NM proceeds by hydroxylation of the 3 and 5 carbons (alpha carbons). However, metabolic alpha hydroxylation of NM has not been previously demonstrated. We incubated NM with rat liver microsomes and an NADPH generating system and demonstrated alpha hydroxylation by isolation of (2-hydroxyethoxy)acetaldehyde as its 2,4-dinitrophenylhydrazone (DNP) derivative. The rate of formation of (2-hydroxyethoxy)acetaldehyde in microsomal incubation mixtures can be assayed by reverse-phase high pressure liquid chromatography (HPLC) of its DNP. When rats were injected with NM, we did not detect (2-hydroxyethoxy)acetaldehyde in the urine, but we did isolate (2-hydroxyethoxy)acetic acid, which presumably resulted from further oxidation. Data will be presented on the deuterium isotope effect for alpha hydroxylation of NM and on the effects of mixed function oxidase inducers on alpha hydroxylation. (no Refs)

5. COMPARISON OF THE IN VITRO METABOLISM OF N-NITROSOHEXAMETHYLENEIMINE BY RAT LIVER AND LUNG MICROSOMAL FRACTIONS.

Hecker LI, McClusky GA
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 42(1):59-64 1982

The in vitro metabolism of N-nitrosohexamethyleneimine by lung and liver microsomes and cytosol from uninduced male Fischer rats is described. Metabolites produced by both organs appeared to be identical. the liver subcellular fractions had a lower Km (0.6 mM) than did lung fractions (3 mM) and metabolized 2.5 to 5x as much nitrosamine per mg protein. Our results, together with those from our earlier studies, indicate that, as the size of the carbon ring increases from nitrosopyrrolidine to nitrosohexamethyleneimine lung microsomes had an increased affinity for the cyclic nitrosamines; there was only a small effect with liver enzymes. This suggests that microsomal enzymes that metabolize cyclic nitrosamines in rat livers and lungs are not the same. the first stable alpha-hydroxylation product, 6-hydroxyhexanal, was not detected in reactions involving microsomes alone. Apparently, this compound is rapidly converted to 1,6-hexanediol by liver or lung microsomes. The presence of cytosol was needed for the full conversion of these metabolites to epsilon-hydroxycaproate and max alpha-hydroxylation activity. Epsilon-Aminocaproate was always found in direct proportion to the hydroxyacid, suggesting that both acids arise from the same alpha-hydroxylation event by different breakdown mechanisms. Beta- and gamma-hydroxynitrosohexamethyleneimine were not metabolized significantly by rat liver enzymes and thus, in this species, may be 'detoxification products' of N-nitrosohexamethyleneimine. (Author abstract) (20 Refs)

6. STUDIES ON NITROSAMINE METABOLISM. III. COMPARISON OF THE SUBCELLULAR DISTRIBUTION OF RADIOACTIVITY IN TISSUES OF RFM AND BALB/C MICE FOLLOWING ADMINISTRATION OF [14C]DIETHYLNITROSAMINE.

Daugherty JP, Clapp NK
Comprehensive Cancer Center, Univ. Alabama Sch. Medicine, Birmingham, AL, 35294
Res Commun Chem Pathol Pharmacol; 34(1):165-168 1981

The tissue distribution of radioactivity in male RFM and BALB/c mice was investigated following a single dose of [14C]-labeled diethylnitrosamine (DEN). The radiolabel was associated with all the subcellular fractions, and the majority of the radioactivity was located in the cytosol fraction. The majority of the radiolabel was usually eliminated from the fractions within 16-24 hr after [14C]DEN administration. (Author abstract) (4 Refs)

7. DISTRIBUTION OF RADIOACTIVITY FOLLOWING ORAL ADMINISTRATION OF CARCINOGENIC 14CH3-LABELLED NITROSOCARBARYL IN THE RAT.

Berand M, Gaillard D, Pipy B, Derache R
Groupe de Recherches sur la Toxicologie des Aliments et des Boissons, INSERM-U87 Universite Paul Sabatier, 2 rue Francois Magendie, 31400 Toulouse, France
Cancer Lett; 14(2):169-174 1981

After a single intragastric dose of 0.25 mg/kg of 14C-N-nitrosocarbaryl (NC) to male Sprague-Dawley rats, radioactivity remaining in various organs after washing with cold NC was determined at 0.5, 3, 7, and 24 hr time intervals. Activity of the blood was high at 0.5 hr after administration and max at 7 hr. Passage of NC across the intestinal barrier was rapid. The very high % of carbaryl extracted from the blood of animals receiving NC po suggested the occurrence of denitrosation. Highest levels of radioactivity were associated with the liver, small intestine, and stomach. Activity in the various organs increased with time up to 7 hr and persisted until 24 hr, except in the forestomach where a rapid decrease was observed between 0.5 and 3 hr. However, the highest concentration of 14C-NC equivalents/mg protein was found in the forestomach. (15 Refs)

8. METABOLISM OF NITROSOACETOXYMETHYLMETHYLAMINE IN LIVER MICROSOMES.

Appel KE, Frank N, Wiessler M
Dept. Toxicology, Inst. Pharmacology, Obere Zahlbacher Str. 67, D-6500 Mainz, W. Germany
Biochem Pharmacol; 30(20):2767-2772 1981

The carcinogen nitrosoacetoxymethylmethylamine (NAMM) was incubated with mouse liver microsomes. The decomposition rate of NAMM and the formation of methanol were determined. After addition of an NADPH-regenerating system, formaldehyde formation resulting from metabolic degradation of the methyl group of NAMM was measured. The results suggest that NAMM is rapidly hydrolyzed by unspecific esterases to nitrosohydroxymethylmethylamine (NHMM). NHMM decomposes according to the activation mechanism of nitrosodimethylamine (NDMA). The formation of methanol proceeds with an even lower velocity. This indicates that intermediate breakdown products - probably NHMM or methyldiazohydroxide (MDH) - possess a distinct stability. Oxidative demethylation of NHMM or MDH was not detectable. The methanol formed is oxidized to formaldehyde by microsomal enzymes. (Author abstract) (31 Refs)

9. CORRELATIONS AMONG THE CHANGES IN HEPATIC MICROSOMAL COMPONENTS AFTER INTOXICATION WITH ALKYL HALIDES AND OTHER HEPATOTOXINS.

Moody DE, James JL, Clawson GA, Smuckler EA
Dept. Pathology, Univ. California Sch. Medicine, San Francisco, CA, 94143
Mol Pharmacol; 20(3):685-693 1981

Male Sprague-Dawley rats were treated with 13 alkyl halides (carbon tetrachloride, bromotrichloromethane, chloroform, bromoform, dichloromethane, dibromomethane, 1,2-dichloroethane, 1,2-dibromomethane, 1-bromo-2-chloroethane, 1,1,2-trichloroethane, 1,2,3-trichloropropane, 1,2-dibromo-3-chloropropane, and 1,2-epoxy-3-chloropropane) and 4 other hepatotoxins (dimethylnitrosamine (DMN), thioacetamide, ethionine, and cadmium acetate) and the content of several microsomal components was assayed. O nly two of the treatments, CCl4 and CBrCl3, resulted in measurable peroxidation of microsomal lipids. These compounds also caused significant decreases in microsomal protein, phospholipid, cytochrome P-450, cytochrome b5, NADPH cytochrome c reductase, stearic acid, and arachidonic acid within 18 hr of treatment. The other alkyl halides tested have higher halocarbon bond-dissociation energies and would be less likely to be metabolized via homolytic cleavage of the halocarbon bonds, which is associated with lipid peroxidation. DMN also had widespread effects on microsomal components but caused no peroxidation of microsomal fatty acids or loss of phospholipid, whereas a significant-

ly lower amount of RNA was recovered from the microsomes. Microsomal responses to the majority of the compounds showed two major similarities: a significant decrease in cytochrome P-450 and a shift in the composition of microsomal fatty acid, primarily characterized by a decrease in arachidonic acid and an increase in linoleic acid. (35 Refs)

10. CONSEQUENCES OF NITROSO COMPOUND FORMATION FROM NITROAROMATIC RADIOSENSITIZERS (MEETING ABSTRACT).

Sridhar R
Oklahoma Medical Research Foundation, Oklahoma City, OK, 73104
Conference on Chemical Modification: Radiation and Cytotoxic Drugs, September 17-20, 1981, Key Biscayne, Florida. Committee for Radiation Oncology Studies 139 pp., 1981.

The feasibility of nitroso compound formation during the metabolism of nitro aromatic compounds such as p-nitrobenzonitrile, 3,5-dinitrobenzonitrile, 2-nitrofluorene, misonidazole and 4-nitroquinoline-N-oxide was tested. The reaction of nitroso compounds with ascorbate, catecholamines (such as isoproterenol, epinephrine and norepinephrine) and reduced glutatione (GSH) gave rise to arylhydronitroxyl free radicals which were detected by electron spin resonance spectroscopy. Aromatic nitroso compounds (ArNO) dramatically accelerated the oxygen consumption by soln of ascorbate, catecholamines and GSH. The corresponding nitro compounds (ArNO(2)) were much less effective than ArNO in stimulating oxygen consumption by these soln. Nitrosoaromatic compounds (ArNO) were found to react with unsaturated lipids such as methyl oleate, phosphatidylcholine and cholesterol in an ene-type manner to yield lipid bound hydroxylamines which underwent easy oxidation to the corresponding arylnitroxyl free radicals. Cytotoxic and mutagenic products are formed during the metabolic reduction of ArNO2. In the presence of oxygen, the reduction does not proceed beyond the ArNO2 ion radical stage since oxygen reacts with this radical to yield superoxide anion radical with concomitant regeneration of ArNO2. Under anaerobic conditions, the reduction can proceed beyond the ArNO2 ion radical stage, but the obligate intermediate, ArNO, is usually not observed because the reduction of th e nitroso compound is easier than the reduction of the parent nitro compound. We have found that hydroxylamines (ArNHOH) are produced during the reduction of ARNO2 by NADPH and rat liver microsomes or by the xanthine-xanthine oxidase system. We have also found that the hydroxylamines are oxidized to ArNO by the horseradish peroxidase - H2O2 system and it is likely that other peroxidases could bring about this reaction. There is precedence in the literature for conversion of arylamines to hydroxylamines by microsomal enzymes. Thus, the action of nitroreductases on ArNO2 followed by the action of peroxidases and other oxygenases could give rise to ARNO. The toxic action of nitroaromatic radiosensitizers may derive, at least in part, from the reaction of ArNO with ascorbate, glutathione, catecholamine and membrane lipids. (no Refs)

11. INTERACTION OF RADIOSENSITIZERS WITH NITROREDUCTASES: BINDING REACTIONS (MEETING ABSTRACT).

Raleigh JA, Liu SF
Radiobiology, Cross Cancer Institute, Edmonton, Alberta, T6G 1Z2, Canada
Conference on Chemical Modification: Radiation and Cytotoxic Drugs, September 17-20, 1981, Key Biscayne, Florida. Committee for Radiation Oncology Studies 139 pp., 1981.

The mechanism of metabolic binding of nitroaromatic compounds to cell constituents both in vitro and in vivo is obscure. Nitroaromatics are known to be reduced to hydroxylamino and amino compounds by nitroreductases. It is conceivable that the putative nitrosoaromatic precursor to the hydroxylamines and amines is the binding species. Nitrosoaromatic compounds are known to bind to thiols, amines and unsaturated lipids. We have shown that nitrobenzene radiosensitizers are reductively bound to unsaturated lipids via a nitroso intermediate in the presence of the nitroreductases, xanthine oxidase and cytochrome C reductase. Even though these same nitroreductases can reductively alter nitroimidazole radiosensitizers, we have been unable to trap a nitroso intermediate with unsaturated lipids. Preliminary experiments with radioactively-labelled misonidazole acetate indicate that binding of the radiosensitizer to the enzyme may be occurring thereby precluding trapping of the binding intermediate by unsaturated lipid or peptides added to the nitroreductase soln. The xanthine oxidase available to us is relatively inactive as a nitroreductase. Under the conditions of the experiment, reduction of misonidazole can occur in air-saturated soln. Presumably, rapid deoxygenation of the soln by xanthine oxidase is efficient which permits subsequent less efficient nitroaromatic reduction to occur. (no Refs)

12. THE DETERMINATION OF O(6)-METHYL- AND 7-METHYLGUANINE IN MOUSE LIVER DNA FROM DIMETHYLNITROSAMINE-TREATED MICE BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY WITH UV ABSORBANCE DETECTION.

Lawrence JF, Leduc R, Ryan JJ
Food Res. Div., Health Protection Branch, Tunney's Pasture, Ottawa K1A 0L2, Ontario, Canada
Anal Biochem; 116(2):433-438 1981

The methylated purines O6-methyl- and 7-methylguanine were isolated from mouse liver DNA hydrolysates by means of a column cleanup employing a Sep Pak C-18 reverse-phase cartridge. The purine bases were eluted from the cartridge with methanol, evaporated to dryness, and then dissolved in mobile phase for liquid chromatographic analysis by normal-phase chromatography. The system consisted of a LiChrosorb Si 60 column with a water-saturated mobile phase of 20% methanol in chloroform containing 0.001% H3PO4. The two methylated bases eluted before adenine or guanine. For extremely low-level (less than 300 pmol) quantitation, the peaks corresponding to O6-methyl- and 7-methylguanine were collected and then analyzed by reverse phase chromatography with LiChrosorb RP-18 column and mobile phase of 5% methanol in pH 7 phosphate buffer (for 7-methylguanine) or 9.5% methanol/buffer (for O6-methylguanine). Comparisons were made with fluorescence detection and with scintillation counting (in animal studies where [14C]dimethylnitrosamine was used). Minimum detectable levels at 254 nm were about 3 ng (3:1 signal to noise ratio) for each of the title compounds. As low as 10 pmol/mg of each could be detected in DNA hydrolysates. Recoveries of O6-methyl- and 7-methylguanine from DNA spiked at 750 pmol/mg were greater than 80%. (Author abstract) (20 Refs)

INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS

13. INVASIVENESS OF HYPERPLASTIC NODULE CELLS FROM DIETHYLNITROSAMINE-TREATED RAT LIVER.

Wanson JC, De Ridder L, Mosselmans R
(c/o Ridder) Lab. Experimental Cancerology, Dept. Radiotherapy, Univ. Hosp., De Pintelaan 135, B-900 Gent, Belgium
Cancer Res; 41(12):5162-5175 1981

Administration of diethylnitrosamine po to female Sprague-Dawley rats induces hepatocellular lesions antecedent to hepatocarcinoma (altered foci and hyperplastic nodules). We have tested hepatocytes from hyperplastic nodules for their invasiveness in vitro, which is a marker for malignancy. The hyperplastic nodule cells are compared with control liver cells and hepatocarcinoma cells. Control liver tissue and the hepatocarcinoma are collected as fragments taken directly from the rat liver. Nodules, on the other hand, isolated by collagenase perfusion of the liver, are collected on a filter. The fragments of normal liver, the nodules, and the hepatocarcinomas were brought in contact with precultured 9-day-old embryonic chick heart fragments for attachment to each other to form confronting cultures. After attachment, the confronting cultures are incubated at 37 C on a gyratory shaker for 24 hr to 14 days. Hepatocytes from the nodules show progressive invasion into the precultured heart fragments in the same way as the hepatocarcinoma cells after 3 to 14 days in vitro. The control hepatocytes from the liver fragments showed no invasion. We conclude from these observations that the cells of the nodules must be considered as malignant altered hepatocytes, for they show progressive invasiveness in vitro. (Author abstract) (38 Refs)

14. PROLIFERATION OF PRENEOPLASTIC LESIONS AFTER DISCONTINUATION OF CHRONIC DEN FEEDING IN THE DEVELOPMENT OF HEPATOMAS IN RAT.

Barbason H, Betz EH
Laboratoire d'Anatomie Pathologique, Universite de Liege au Sart Tilman, Tour de Pathologie, 4000 Liege, Belgium
Br J Cancer; 44(4):561-566 1981

The compound diethylnitrosamine (DEN, 10 mg/kg/day) was fed to rats for 2, 4, and 6 wk. At different times after feeding with DEN was stopped, growth of preneoplastic lesions has been correlated with pathological evolution (preneoplastic foci, neoplastic nodules and hepatomas). The proliferating fraction in the foci, the cell content, and relative vol of foci increase as a function of the duration of the treatment. The proliferating fraction increases evenly throughout the liver, but, in all experimental modalities, preneoplastic cells show a proliferative advantage over the phenotypically normal tissue. In each experimental group, the proliferative rate correlates with the pathological evolution. After 2 wk of DEN feeding the growth activity of foci remains very low, and neoplastic nodules are not detectable until the median time of death (14 mo). After 4 and 6 wk, a critical size of the foci is reached, corresponding to the neoplastic transformation, and an increased labeling index is triggered in the lesions and in the phenotypically normal tissue. It is speculated that the 'growth pressure' induced by the first carcinogen treatment, associated with the subsequent disturbance of the mitotic control regulation, may be implicated in the process of malignant transformation of preneoplastic lesions. (Author abstract) (13 Refs)

15. DISTRIBUTION OF NUCLEAR SIZE AND DNA CONTENT IN SERIAL LIVER BIOPSIES OF RATS TREATED WITH N-NITROSOMORPHOLINE, PHENOBARBITAL AND BUTYLATED HYDROXYTOLUENE.

Romagna F, Zbinden G
Inst. Toxicology, Swiss Federal Inst. Technology, Univ. Zurich, Schorenstrasse 16, CH-8603 Schwerzenbach, Switzerland
Exp Cell Biol; 49(6):294-305 1981

Nuclear size distribution and DNA content distribution were determined in liver biopsies of rats using an electronic particle counter and an impulse cytophotometer, respectively. Nuclear size distribution and DNA content distribution were found to be highly correlated regardless whether peak areas or peak heights of the histograms were compared. Treatment with the hepatocarcinogen N-Nitrosomorpholine (NNM) caused a dose-dependent increase in octoploid nuclei and a shift of the 2 n:4 n ratio in favor of the diploid nuclei. Treatment with Pb and BHT had minor effects on nuclear size and DNA content distribution. The paper demonstrates the usefulness of fine-needle aspiration biopsy procedure for the evaluation of liver changes induced by chemical substances. (Author abstract) (13 Refs)

16. CYTOCHEMICAL AND BIOCHEMICAL MICROANALYSIS OF CARCINOGENESIS.

Bannasch P, Benner U, Hacker HJ, Klimek F, Mayer D, Moore M, Zerban H
Abteilung fur Cytopathologie, Institut fur Experimentelle Pathologie, Deutsches Krebforschungszentrum, D-6900 Heidelberg 1, W. Germany
Histochem J; 13(5):799-820 1981

The use of analytical cytochemistry, enzyme cytochemistry, autoradiography, microdissection, and biochemical microanalysis in the elucidation of mechanisms of cell transformation is reviewed. The first cytopathologic phenomenon which can be detected by cytochemical means during the process of hepatocarcinogenesis is an excessive storage of glycogen. Hepatocellular glycogenesis is related to the dose and time of carcinogen treatment and to the development of hepatocellular tumors. A sequence of cellular changes has been established leading from the glycogen-rich hepatocyte, which appears clear or acidic in hematoxylin/eosin sections, to the basophilic hepatoma cell, which is poor in glycogen but rich in ribosomes. Excessive storage of polysaccharides or lipids is correlated with the development of other tumors as well, including renal epitheliomas induced in rats by oral application of nitrosomorpholine. Three types of epithelial kidney tumors develop under these conditions, all with specific histogenesis and cytogenesis. Extensive light-, electron- and fluorescent micrographs illustrate the text. (68 Refs)

17. DOSE RESPONSE STUDIES OF CARCINOGENESIS IN RATS BY NITROSODIETHYLAMINE.

Lijinsky W, Reuber MD, Riggs CW
Chemical Carcinogenesis Program and Information Systems Dept., Frederic Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 41(12):4997-5003 1981

A dose-response study was conducted in Fischer rats with nitrosodiethylamine, which was administered in regulated amounts as a soln in drinking water. Groups of 20 female rats each received a different treatment; one group consisted of 12 animals; one of the groups was untreated. The concentrations of the soln fed ranged from 113 to 0.45 mg/liter at six successive concentrations differing by a factor of 2.5. The treatment

times were 17 wk at the highest concentration; 22 wk with 45 mg/liter; and 30 wk with 18, 7, 2.8, 1.1 and 0.45 mg/liter. The two lowest dose levels were also given for 60 wk, and the 0.45-mg/liter dose levels were also given for 104 wk. Animals were allowed to die naturally with tumors, and the time to death with tumors was an index of the potency of treatment. In the top four treatment groups, the potency measured in this way was proportional to the total dose of carcinogen administered. At all other doses, survival time was much less dependent on the dose administered, whether or not tumors were induced by the treatment. The principal tumors found were in the upper gastrointestinal tract, mainly the esophagus, at all doses. In the two highest dose groups, there was a high incidence of liver tumors also. There were few liver tumors in the lower dose groups, but there was a dose-related incidence of tumors of the upper gastrointestinal tract. It was remarkable that a nitrosodiethylamine concentration of 0.45 mg/liter (0.45 ppm) administered for 104 wk induced tumors of the upper gastrointestinal tract in 70% of the treated rats. (Author abstract) (15 Refs)

18. RELATIONSHIP OF RAT URINARY METABOLITES OF N-NITROSOMETHYL-N-ALKYLAMINE TO BLADDER CARCINOGENESIS.

Singer GM, Lijinsky W, Buettner L, McClusky GA
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 41(12):4942-4946 1981

Nitrosomethylalkylamines with chain lengths from C4 (n-butyl-) to C14 (n-tetradecyl-) were each administered to three rats at doses equimolar with 12 mg of the butyl compound. All of the compounds administered to rats at this dose, twice a wk for 30 wk, induced tumors in 100% of the animals. Some of the compounds with even-numbered alkyl chains induced bladder tumors, and a connection was sought with the metabolites of these excreted in urine. The pooled 24-hr urine was extracted with ethyl acetate before and after acidification to provide a neutral fraction and a fraction containing nitrosamino acids. The fraction containing the acids was analyzed by capillary gas chromatography and by gas chromatography-mass spectrometry after esterification with diazomethane; the neutral fraction was analyzed similarly. The principal metabolite of the nitrosamines with odd-numbered chains was found in the acidic fraction and was identified as nitrosomethyl-2-carboxyethylamine. There were several acids in the mixtures derived from the nitrosamines with even-numbered chains, nitrososarcosine and nitrosomethyl-3-carboxypropylamine being the major components. There was no trend in the yields of the nitrosamino acids that could be correlated with the differences in carcinogenic potency between the nitrosamines; the max yield of acids was more than 30% (from the tetradecyl compound). The principal component of the neutral fraction (+-1% of the nitrosomethylalkylamine administered) was nitrosomethyl-2-oxopropylamine. The yield of this compound increased with increasing length of the even-numbered chain nitrosamines. (Author abstract) (14 Refs)

19. THE EFFECT OF 4-SUBSTITUTION ON THE CARCINOGENICITY OF NITROSOPIPERIDINE.

Lijinsky W, Singer GM, Reuber MD
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21 701
Carcinogenesis; 2(10):1045-1048 1981

Nitrosopiperidine (NPIP), 4-phenylnitrosopiperidine, 4-cyclohexylnitrosopiperidine, and 4-tertiary-butylnitrosopiperidine were administered at equimolar (0.88) concentrations in drinking water, 5 days/wk, to groups of 20 female Fisher 344 rats, for 50-60 wk. Like NPIP, both 4-phenyl- and 4-tertiary-butyl-NPIP induced esophageal papillomas and carcinomas in almost all animals, although time to death with tumors was considerably longer with the phenyl compound and still longer with the tertiary-butyl compound. Forestomach carcinomas occurred in 2/20 animals treated with 4-tertiary-butyl NPIP but in none of the animals treated with the other three compounds. Only 4-phenyl-NPIP induced liver tumor, 7 angiosarcomas and 14 hepatocellular carcinomas. Tongue papillomas (5) or carcinomas (7) occurred only in rats treated with 4-tertiary-butyl-NPIP. In general, NPIP induced tumors more quickly after administration of a smaller total dose than the other three compounds. The results indicate that all three derivatives of NPIP are considerably less carcinogenic than NPIP itself and that the 4-cyclo-hexyl derivative had no carcinogenic activity at the dose studied. The fact that only the 4-phenyl derivative induced liver tumors may be related to formation of phenolic compounds. (11 Refs)

20. FORMATION OF TISSUE-BOUND N'-NITROSONORNICOTINE METABOLISM BY THE TARGET TISSUES OF SPRAGUE-DAWLEY AND FISHER RATS.

Brittebo EB, Tjalve H
Dept. Toxicology, Univ. Uppsala, Box 573, S-751 23 Uppsala, Sweden
Carcinogenesis; 2(10):959-963 1981

The way in which N'-[14C]nitrosonornicotine (NNN) selectively induces tumors in the nasal cavity and esophagus in Sprague-Dawley and Fisher rats was investigated. No major differences in distribution of radioactivity was seen in the two strains. In vivo and in vitro autoradiographic studies following iv injection of 14C-NNN demonstrated localization of tissue-bound metabolites in the mucosa of the nasal cavity, esophagus, tracheo-bronchial tree, and tongue. High levels of unbound radioactivity were found in Zymbal's gland and submaxillary, preputial, lacrimal, and tarsal glands. In vitro experiments in which tissue slices were incubated with 3 uM 14C-NNN, demonstrated marked formation of tissue-bound NNN metabolites by nasal mucosa, liver, and esophagus. Liver tissue also formed bound NNN metabolites, but to a lesser extent than nasal mucosa, whereas levels of bound metabolites in esophagus cultures were almost undetectable. The results suggest that in situ metabolic activation of NNN plays an important role in the pathogenesis of NNN-induced tumors. (13 Refs)

21. ENHANCING EFFECTS OF DIMETHYLNITROSAMINE ON AFLATOXIN B1 HEPATOCARCINOGENESIS IN RATS.

Angsubhakorn S, Bhamarapravati N, Romruen K, Sahaphong S
Dept. Pathobiology, Faculty Science, Mahidol Univ., Rama 6 Road, Bangkok 4, Thailand
Int J Cancer; 28(5):621-626 1981

In a study of possible enhancing effects of dimethylnitrosamine (DMN) on aflatoxin B1 (AFB1) hepatocarcinogenesis, male Buffalo strain rats were fed diets containing 1 ppm AFB1, 25 ppm DMN, and a combination of 1 ppm AFB1 and 25 ppm DMN (AFB1 + DMN). The diets were replaced by chow pellets after 6 mo, and animals were killed 3, 6, 9 and 12 mo after the onset of the experiment. In the untreated control group animals were free of hepatocellular carcinoma but the treated groups fed AFB1, DMN and AFB1 plus DMN developed he-

patic lesions ranging from multiple cysts, altered cell foci and neoplastic nodules to hepatocellular carcinomas. Hepatocellular carcinomas developed in 79%, 45% and 5% of rats fed AFB1 plus DMN, AFB1 and DMN respectively at the end of the experiment. Multiple cysts were also found in all periods in animals fed AFB1 plus DMN, whereas rats fed AFB1 and DMN separately developed a few multiple cysts by the end of the experiment. These findings suggest that DMN potentiates the hepatocarcinogenesis induced by AFB1 in rats. (Author abstract) (28 Refs)

22. THE CHEMISTRY OF ACTIVATED INTERMEDIATES OF N-NITROSO COMPOUNDS CONTAINING THE 2-OXOPROPYL GROUP (MEETING ABSTRACT).

Nagel D, Wallcave L, Mirvish S, Smith J
Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, NE, 68105
Newsletter Natl Pancreas Cancer Project; VI(2):43 1981

To date all N-nitrosamines which contain or are metabolized to nitrosamines containing a 2-oxopropyl group have been shown to induce pancreatic adenocarinoma in the Syrian hamster. Within this series of nitrosamines bis(2-oxopropyl)nitrosamine (BOP) is the most specific for the hamster pancreas while methyl-2-oxopropyl-nitrosamine (MOP) is the most potent (MOP induces tumors in the hamster pancreas and other organs with a single dose of 2.5 mg/kg). In vivo alkylation studies have shown that BOP predominantly methylates pancreatic DNA while liver DNA is both methylated and alkylated with a longer alkyl group of unknown nature (perhaps a 2-oxopropyl group). Two mechanisms of activation of BOP appear plausible. (1) BOP is metabolized to MOP which in turn is alpha hydroxylated yielding either a methylating or 2-oxopropylating species which can react with cellular macromolecules including DNA, producing methylated or oxopropylated adducts. 2) Alternatively BOP is alpha hydroxylated and decomposes by two different routes. The classical decomposition pathway would lead to a 2-oxopropylating species while a second competing pathway would lead to a methylating species. To test these hypotheses we have prepared ethyl-N-nitroso-2-oxopropylcarbamate (OPC) and the two alpha acetoxy derivatives of MOP [N-acetoxymethyl-N-2-oxopropylnitro samine (AMOP) and N-methyl-N-(1-acetoxy-2-oxopropyl)amine (MAOP)] and studied their soln chemistry and reactions with selected nucleophiles. OPC reacts with 3,4-dichlorothiophenol producing both methylated and oxopropylated thioethers supporting the second hypothesis while the extreme reactivity of MAOP in solvolysis studies in comparison to alpha-acetoxydimethylnitrosamine tends to support the first hypothesis. (no Refs)

23. METABOLISM OF N-NITROSO-2,6-DIMETHYLMORPHOLINE (NNDM) BY THE VARIOUS COMPONENT CELLS OF HAMSTER PANCREAS (MEETING ABSTRACT).

Scarpelli DG, Rao MS, Kokkinakis D, Hollenberg P
Department of Pathology, Northwestern University Medical School, 303 E. Chicago Avenue, Chicago, IL, 60611
Newsletter Natl Pancreas Cancer Project; VI(2):52 1981

Hamster pancreas contains the necessary enzymes for activation of NNDM and N-nitrosobis(2-oxopropylamine) (NBOP) to forms mutagenic for Salmonella typhimurium. We report here on the metabolism of [3H]NNDM by S-9 and microsomes of whole pancreas (WP), and highly purified fractions of acinar cells (AC), and S-9 of islet cells (IC) isolated from normal and tetrachlorodibenzoparadioxin (TCDD) treated pancreas. Metabolism by duct and ductal cells was established by incubation of pancreatic slices in medium containing NNDM in the presence of [3H] thymidine with and without hydroxyurea to assess DNA repair. Analysis of metabolites by high pressure liquid chromatography showed that S-9 of WP, AC and IC metabolize NNDM to the following sequences of compounds respectively in descending order of concentration: N-nitroso(2-hydroxypropyl-2-oxopropyl)amine (HPOP) greater than NBOP greater than nitrosobis(2-hydroxypropyl)amine (BHP); NBOP greater than HPOP greater than BHP; and NBOP greater than BHP greater than HPOP. Addition of NADPH did not significantly alter metabolism of WP, but for AC led to increased formation of BHP; pretreatment with TCDD increased total metabolism in all instances. Microsomes of WP and AC produced the sequence NBOP greater than BHP greater than HPOP. TCDD increased (78%) total metabolism over that of controls. NADPH led to increased metabolism with both control microsomes (228%) and those isolated from TCDD pretreated animals (212%). Metabolism by S-9 and microsomes isolated from WP, AC and IC were about 1/20 those isolated from liver. Unscheduled DNA synthesis (repair) in nuclei of duct epithelium suggests that these cells are also capable of metabolizing NNDM. (1 Ref)

24. TISSUE AND SPECIES DIFFERENCES IN THE ABILITY OF THE PANCREATIC CARCINOGEN N-NITROSOBIS(2-OXYPROPYL)AMINE (BOP) TO INDUCE DNA DAMAGE (MEETING ABSTRACT).

Lawson T
Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, NE, 68105
Newsletter Natl Pancreas Cancer Project; VI(2):32 1981

The production of DNA damage is a measure of a carcinogen's ability to induce po tentially mutagenic and carcinogenic lesions in DNA. The ability of the carcinogen BOP to produce such lesions has been compared in target and non-target tissues of Syrian hamsters and MRC rats. In hamsters, BOP's carcinogenicity was dose-dependent, producing only pancreatic tumors at lower doses and also liver tumors at higher doses. In rats, BOP's carcinogenicity depended on the route of administration, and resulted in liver and colo-rectal tumors when given sc and prostate tumors when given po. Extensive DNA damage was produced in hamsters by 10 mg BOP/kg in the pancreas (target tissue) and the liver and salivary gland (non-target tissues). BOP persisted longer in the pancreas. At higher doses (20 and 40 mg/kg) persistance of damage was also seen in the liver. For the DNA damage in the pancreas there was an impressive dose response and a close correlation with the carcinogenicity of BOP. In rats, no DNA damage was seen in the pancreas (non-target tissue). The tissues in which BOP is a carcinogen all exhibited extensive and persistent DNA damage (liver, colon and prostate). These studies are being complemented by examinations of the in vivo metabolism of BOP and the nature and extent of alkylation produced. These results indicate that a potent carcinogen such as BOP is capable of producing potentially carcinogenic lesions in a variety of tissues, but that the subsequent carcinogenicity depends on one or more other factors, such as the capacity to produce a mitogenic response which will stimulate the tissue to cell division to 'lock in' the carcinogenic lesion. (no Refs)

25. INDUCTION OF PANCREATIC DNA DAMAGE AND TUMORS IN RATS TREATED WITH N-NITROSO-BIS(2-OXOPROPYL)AMINE (MEETING ABSTRACT).

Longnecker DS, Zurlo J, Curphey TJ
Department of Pathology, Dartmouth Medical School, Hanover, NH, 03755
Newsletter Natl Pancreas Cancer Project; VI(2):35 1981

Differences in response of various species to carcinogens pose problems in regard to extrapolation from animal experiments to man. In experimental pancreatic carcinogenesis, several oxidized derivatives of dipropylnitrosamine have been effective pancreatic carcinogens in hamsters whereas they have failed to induce pancreatic cancers in rats. In studying this species difference we have used alkaline elution analysis to demonstrate DNA damage in pancreas of rats treated with N-nitrosobis(2-oxopropyl)amine (BOP) and N-nitroso-(2-hydroxypropyl-2-oxopropyl)amine (HPOP). Because these agents were effective in inducing DNA damage in pancreas, we treated young rats with a single dose of BOP (100 mg/kg) or HPOP (20 mg/kg) and autopsied them 4 mo later. Grossly visible nodules measuring up to 3 mm were present in pancreases of rats of both groups. Histologically the pancreases contained multiple foci and nodules of atypical acinar cells which were not seen in controls. Thus, BOP and HPOP induce both DNA damage and phenoty pic changes in acinar cells in rats which are similar to those induced by the pancreatic carcinogens azaserine and Ndelta-(N-methyl-N-nitrosocarbamoyl)-L-ornithine. Although rats appear to be less sensitive than hamsters to BOP, both species respond to comparable doses of HPOP. Our findings suggest that these compounds would induce pancreatic cancers in rats in studies of 1-2 yr duration if appropriate doses are given to young rats. (no Refs)

26. A STUDY OF THE ORGAN DISTRIBUTION AND BINDING OF 1-METHYL-1-NITROSOUREA (MNU) AND 1-METHYL-3-NITRO-1-NITROSOGUANIDINE (MNNG) AFTER ORAL ADMINISTRATION IN THE GUINEA PIG (MEETING ABSTRACT).

Woolley PV, Yerino P
Division of Medical Oncology, Georgetown University Medical Center, Washington, DC, 20007
Newsletter Natl Pancreas Cancer Project; VI(2):67 1981

The induction of pancreatic carcinoma in the guinea pig by the oral administration of MNU is an important animal model for this disease. Much of our effort is directed at an analysis of this system and at a comparison of MNU with the related compound MNNG, which is a gastric carcinogen rather than a pancreatic carcinogen after oral administration. In this study we have compared directly the distribution of these two agents in the guinea pig. Each drug synthesized with 14C in either the methyl group or the carbonyl (guanidino) carbon and these separate preparations were given as a single oral dose of 0.1 mmoles/kg body wt. Organ uptake as a function of time was expressed as total and acid-insoluble radioactivity. Alkylation was estimated as the radioactivity in DNA, RNA and protein fractions and confirmed by measuring the formation of 7-methylguanine on high pressure liquid chromatography. Widespread distribution of these drugs was measurable. Highest levels of all 4 drug labels were found in the liver. For other organs, including the pancreas, peak whole tissue levels ranged from 10-50 nmoles/g, of which 20-30% was TCA-precipitable. In the stomach, alkylation of DNA and RNA was comparable for MNU and MNNG, but in all other organs MNU binding was 2-10 fold greater than MNNG. This difference was very evident in the pancreas. Binding of MNU in the pancreas was comparable to that in other organs and persisted at least 24 hr. The data show that the pancreas and other organs are readily modified by the oral administration of MNU. They support the idea that MNU would be a more potent pancreatic carcinogen than MNNG, in agreement with earlier data in pancreatic lobules. (no Refs)

27. MORPHOLOGIC EFFECT OF N-NITROSO-BIS(2-OXOPROPYL)AMINE (BOP) ON HAMSTER PANCREATIC DUCTS IN CULTURE (MEETING ABSTRACT).

Githens S, Whelan JF, Ruby JR
Department of Biological Sciences, University of New Orleans, New Orleans, LA, 70148
Newsletter Natl Pancreas Cancer Project; VI(2):22 1981

Isolated hamster pancreatic ducts in culture were exposed either once at the beginning of the culture period, or twice-weekly, to a range of BOP concentrations. Single doses of 5 ug/ml or twice-weekly doses of 1 ug/ml were toxic to interlobular ducts but less so to intralobular ducts as revealed by gross appearance and histological and autoradiographic analysis. Nuclear enlargement was frequently observed. Lower doses caused no obvious alterations in morphology or growth in culture. No BOP-induced effects were observed with ducts from hamsters previously injected with beta-naphthoflavone to induce BOP metabolizing enzymes. Ducts exposed to epidermal growth factor (EGF) to enhance DNA synthesis, or to the tumor promoter 12-O-tetra decanoyl phorbol-13-acetate, did not exhibit any obvious BOP-induced changes. BOP effects were initiated in vivo by injecting hamsters with 20 mg BOP per kg body wt and ducts were isolated one wk later in the usual manner. These ducts were maintained in culture for up to 20 wk. In one experiment a number of duct fragments exhibited mucus or goblet cell metaplasia and ultrastructural changes similar to those reported by others in BOP-induced hamster pancreas adenocarcinoma in vivo. Ducts treated in culture with 2 ug/ml BOP twice weekly for 8 wk and injected into athymic nude mice survived and also exhibited goblet like cells when the mice were sacrificed 7 mo later. Untreated ducts injected into nude mice did not exhibit such changes. The treated ducts were not, however, neoplastic. (no Refs)

28. A STUDY OF THE EFFECTS OF 1-METHYL-1-NITROSOUREA (MNU) ON THE PHYSICAL PROPERTIES OF CHROMATIN IN THE GUINEA PIG PANCREAS (MEETING ABSTRACT).

Yang P, Woolley PV
Division of Medical Oncology, Georgetown University Medical Center, Washington, DC, 20007
Newsletter Natl Pancreas Cancer Project; VI(2):67 1981

The literature indicates that carcinogens can alter the physical state of chromatin in target tissues. As a part of the study of carcinogen effects upon the pancreas and other organs, we have examined the effect of MNU administration on the thermal melting and circular dichroism spectra of pancreas and liver chromatin. Oligomeric chromatin (av DNA size 2000 base pairs) was isolated from purified nuclei by a mild nuclease digestion, followed by a 5-20% linear sucrose gradient centrifugation, and was dialyzed into 1mM Tris, pH 8 for examination of thermal melting. The melting curves were broad and when expressed in derivative form showed several distinct melting regions, with Tm values of 56, 64 and 78 C. When animals were treated with 10 mg/kg MNU, there was no effect on either the thermal melting profile or the circular dichroism spectrum of pancreatic chromatin, but with 60 mg/kg three x

in eight days, there were definite shifts of melting towards lower temperatures. The effect was more pronounced in the pancreas than in the l iver. There were small concurrent changes in the circular dichroism spectra. The data indicate that MNU can produce alterations in the physical state of pancreatic chromatin and that the pancreas may be more easily damaged than the liver. (no Refs)

29. AUGMENTATION OF CARCINOGENESIS BY N-NITROSOBIS(2-OXOPROPYL)AMINE (NBOP) ADMINISTERED DURING S PHASE IN REGENERATING HAMSTER PANCREAS (MEETING ABSTRACT).

Scarpelli DG, Rao MS, Subbarao V
Department of Pathology, Northwestern University Medical School, 303 E. Chicago Avenue, Chicago, IL, 60611
Newsletter Natl Pancreas Cancer Project; VI(2):51 1981

It is noteworthy that ductal adenocarcinomas develop so readily in pancreas where ductal cells constitute only 4% of its voi, as contrasted to acinar cells which represent 82% of the total vol. The exclusive development of ductal adenocarcinoma in hamster following chronic exposure to carcinogens could be due to either a greater sensitivity of ductal epithelium, or to a histogenetic pathway for tumorigenesis involving acinar cells. The present experiments were undertaken to ascertain the neoplastic potential of acinar cells in hamster pancreas. This was accomplished by administering NBOP to regenerating pancreas when the max number of acinar cells are in S phase, as compared to only rare islet and duct cells. Regeneration was induced with ethionine in 30 5-6 wk old hamsters. These were divided into 2 groups, which were treated as follows: Group I 30 mg NBOP/kg body wt given at 60 hr of regeneration followed by 10 mg/kg body wt/wk for 9 wk; Group II 5 mg NBOP/kg body wt at 60 and 66 hr followed by 10 mg/kg body wt/wk for 8 wk. Three groups of animals consisting of 10 each, with normal pancreas served as controls; Group III received NBOP at doses as scheduled for Group I; Group IV received NBOP at doses as scheduled for Group II; and Group V received 10 mg NBOP/kg body wt/wk for 10 wk. Animals were sacrificed when moribund or at 26-28 wk. Pancreatic ductal adenocarcinomas were induced in all groups. However, the yield of tumor varied as follows: Grp I, 63%; Grp II, 20%; Grp III, 20%; Grp IV, 20%; Grp V, 27%. In each instance, these were invasive lesions. In many animals neoduct formation was evident in acini. The foregoing is additional support for the notion that under appropriate stimulus, acinar cells can modulate to ductal epithelium and may be involved in the development of ductal adenocarcinoma. (no Refs)

30. MODIFYING FACTORS IN PANCREATIC CARCINOGENESIS IN THE SYRIAN HAMSTER MODEL. I. THE EFFECT OF DUCT LIGATION AND PARTIAL PANCREATECTOMY (MEETING ABSTRACT).

Pour PM, Donnelly T
The Eppley Institute for Research in Cancer, University of Nebraska, Medical Center, Omaha, NE, 68105
Newsletter Natl Pancreas Cancer Project; VI(2):47 1981

By examining the effect of pancreatic duct ligation and partial pancreatectomy o n the overall pancreatic carcinogenicity of a single injection of N-nitrosobis(2-oxopropyl)amine (BOP), it was found that the incidence and the multiplicity of tumors were significantly decreased after both tvpes of surgery when BOP was given immediately after th nd closure, but not when BOP was given later, ie after 3 d s or 1 wk. For example, 62% of all hamsters treated wit. BOP one wk after partial pancreatectomy developed tumors, whereas only 8% of those receiving the same dose immediately after surgery showed the equivalent neoplasms. In comparison, a 60% tumor incidence occurred in hamsters not operated upon or which received the carcinogen later than 3 days after the surgery. It is interesting that a similar pattern was also observed in sham-operated BOP-treated hamsters. The pattern of benign and malignant tumors induced by each procedure will be presented, and the possible reasons for inhibition of tumor development by surgery will be discussed. (no Refs)

31. PROTECTIVE EFFECT OF ETHANOL ON THE DEVELOPMENT OF PANCREATIC CANCER (MEETING ABSTRACT).

Tweedie JH, Reber HA, Pour P
No affiliation given
Newsletter Natl Pancreas Cancer Project; VI(2):61 1981

We examined the effects of chronic ethanol ingestion on pancreatic function and the appearance of pancreatic neoplasms in hamsters. Three groups of animals were fed standard laboratory chow and water ad lib. Group 1 received no other treatment. Group 2 received a single injection of N-nitrosobis(2-oxopropyl)amine (BOP) (20 mg/kg sc), a dose known to produce pancreatic carcinomas within 28 wk. Group 3 had ethanol added to the drinking water (25% wt/vol) for the duration of the study, and received the same dose of BOP 2 wk after starting the ethanol treatment. After 24 wk, pancreatic juice was collected following secretin and cholecystokinin stimulation, and the pancreases were examined histologically by one of us who had no knowledge of the treatment regimen. The presence of ductal proliferation (Proliferative Index, PI) and neoplastic lesions (adenoma, carcinoma in situ, carcinoma) was recorded. The blood ethanol concentration was 130 +/-8 mg% in Group 3 animals. Chronic ethanol ingestion was associated with significantly less preneoplastic ductal proliferation and fewer neoplastic pancreatic lesions. The explanation for this observation is uncertain, but it may be related to ethanol's known ability to alter the metabolism of pancreatic secretory cells. Thus the carcinogen may have been metabolized differently in these animals. (no Refs)

32. TISSUE-DEPENDENT ENZYME-MEDIATED REPAIR OR REMOVAL OF O-ETHYL PYRIMIDINES AND ETHYL PURINES IN CARCINOGEN-TREATED RATS.

Singer B, Spengler S, Bodell WJ
Dept. Molecular Biology, Univ. California, Berkeley, CA, 94720
Carcinogenesis; 2(10):1069-1073 1981

Ten-day-old BD IX rats were injected with radiolabeled N-ethyl-N-nitrosourea (Et NU: 69.4 ug/kg, ip), and the sites and proportions of ethyl products, as well as their removal and repair, in DNA from various tissues was examined. One hr after carcinogen injection, DNA of brain, liver, and other pooled organs (spleen, lung, thymus, muscle, and intestine) showed similar proportions of the derivatives quantitated (O6-ethyl [Et] guanine [G], 7EtG, 3-Et adenine [A], O2-Et thymine [T], O4-EtT, O2-Et cytosine [C], and ethylphosphotriesters). During the 75 hr after carcinogen administration, most ethylated bases were poorly removed (or, in the case of O4-EtT, not at all) from DNA in the brain (the target tissue of EtNU carcinogenicity), and from DNA in the tissue pool. Removal from the brain appeared to cease after 25-50 hr. Kinetics of O6-EtG removal in brain and in the tissue pool were similar, except that there was a rapidly exhausted early and partial repair capability in brain. O-alkyl products were removed from the liver at progressively increasing rates over the entire 75-hr

period. The accelerated loss of O2-EtT, O4-EtT, and O2-EtC may have been due either to an increase in hepatic protein synthesis as a result of recovery from EtNU-induced inhibition or to induction of an O-alkyl pyrimidine-specific enzyme. Triester levels remained almost unchanged in all tissues examined. However, the small decrease in the triester level observed in liver DNA suggested a half-life of greater than 1 wk. Any or all persistent promutagenic derivatives (O6-EtG, O2-EtT, O4-EtT, O2-EtC) may be important in initiation of carcinogenesis by somatic mutation. (45 Refs)

33. ULTRASTRUCTURE OF PULMONARY TUMORS INDUCED IN RATS BY N-NITROSOMETHYLURETHANE.

Reznik-Schuller HM, Hague BF, Creasia DA
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
J Toxicol Environ Health; 8(3):501-506 1981

Intraperitoneal injections of N-nitrosomethylurethane (NMU: 5 mg/kg, 1x every other wk for 3 mo) induced multiple adenomas in the lung periphery of five female Fisher (F344) rats. Electron microscopy revealed two different types of lamellar bodies; one had crossbars and the other had concentrically arranged parallel lamellae. Lamellar bodies in the healthy animal are a typical feature of alveolar type II cells. The findings suggest that NMU-induced lung tumors originate from the alveolar type II cells in these rats. (10 Refs)

34. CYTOLOGIC FINDINGS IN CARCINOGEN-INDUCED CANINE LUNG TUMORS (MEETING ABSTRACT).

Yokota S, Pak HY, Teplitz RL, Benfield JR
City of Hope National Medical Center, Duarte, CA
Acta Cytol (Baltimore); 25(4):455 1981

Early detection of cancerous lesions of the lung is our ultimate goal and common interest. In order to better evaluate and understand the progression of changes in the development of lung neoplasia, a canine lung cancer animal model has been developed over the past six yr. This model was chosen for several reasons, including lending itself to the same procedural manipulations as used in humans, the feasibility and predictable induction of lung cancer at preselected sites and the rate of natural development of lung neoplasms. To date, ten separate protocols using different carcinogens, doses and techniques have been employed. These include: benzo(a)pyrene (BP), nitrosomethyl-urea (NMU), dimethylbenzanthracene (DMBA), methylcholanthrene (MCA) and 91Ybeta radiation. These carcinogens have been introduced by intrabronchial and intrapulmonary sustained release implants of DMBA and 91Ybeta, respectively, and serial intrabronchial submucosal or topical application of aromatic hydrocarbons (BP, DMBA, MCA and NMU). Ten of 89 dogs enrolled in five of the ten protocols have developed lung neoplasms, all of which have been confirmed with histology. This paper describes the cytologic findings of the serial bronchial brushings and washings spanning preinduction of the carcinogens to the development of the lung neoplasms. (no Refs)

35. MITOCHONDRIAL ANOMALIES IN RENAL ONCOCYTES INDUCED IN RAT BY N-NITROSOMORPHOLINE.

Krech R, Zerban H, Bannasch P
Abteilung fur Cytopathologie, Deutsches Krebsforschungszentrum, D-6900 Heidelberg 1, W. Germany
Eur J Cell Biol; 25(2):331-339 1981

Renal oncocytes were induced in male Sprague-Dawley rats by oral application of N-nitrosomorpholine (NNM) in concentration of 12 or 50 mg/100 ml drinking water and analyzed by transmission electron microscopy. The oncocytes exhibited mitochondrial anomalies which were very similar to those of human oncocytoma oncocytes. The most striking mitochondrial changes were an unusually large number of the organelles and an excess of the cristae mitochondriales. The shape of the mitochondria varied from round and oval to extremely elongated slender or cup-shaped organelles often piled up to form complex bodies. Rarely large ramifying mitochondria were found. In addition to transversely orientated cristae or tubules the inner mitochondrial membranes frequently formed dense stacks of unusually long cristae often arranged longitudinally. In some mitochondria straight and strictly parallelly arranged neighboring cristae were found to be connected by a paracrystalline array of pillars bridging the mitochondrial matrix. In the majority of oncocytes the mitochondrial matrix contained prominent dense granules (diameter 30-50 nm), but sometimes these were rare or absent. Individual mitochondria of many oncocytes showed membrane-bound deposits of glycogen particles which usually formed rosettes with a diameter of about 80 nm. Partitioned mitochondria were not seen. Often autophagic vacuoles containing portions of degraded mitochondria and dense bodies, probably autophag osomes, were observed. The nature and significance of the oncocytes remains unclear, but we suggest from these and earlier experimental results that oncocytes represent a special type of a neoplastically transformed cell which usually has only a low potential for 'autonomous' growth. Renal oncocytes induced in rats by chemical carcinogens appear to be an excellent experimental model for the further investigation of this cell type. (Author abstract) (46 Refs)

36. IMMUNOPEROXIDASE STUDIES ON A TUMOR-CELL-ASSOCIATED ANTIGEN(S) IN RAT RENAL NEOPLASMS INDUCED BY DIMETHYLNITROSAMINE.

Yantchev IK
Inst. General and Comparative Pathology, Bulgarian Acad. Sciences, Sofia-1113, Bulgaria
Neoplasma; 28(4):447-455 1981

Renal neoplasms were induced in rats of Wistar line by a single, ip injection of dimethylnitrosamine (60 mg/kg). The histological investigation indicated that these tumors were entirely mesenchymal in nature. In some of them (16.6%) small adenocarcinomas were seen. Immunological studies were carried out by light and electron microscope, using the immunoperoxidase 'bridge' technique. Tumor cell-associated antigen(s) was detected in 62% of the neoplasms examined. This antigen was individual as it did not react with sera from the other tumor bearing rats. It was established that this antigen was located mainly on the plasma membrane and also, even though in a lesser degree, on the endoplasmic reticulum and nuclear envelope of the tumor cells of mesenchymal and epithelial origin. Except the existence of tumor cell-associated antigen(s) in these neoplasms, the presence of antibodies produced against them in the sera of the diseased rats were also detected by these investigations. (Author abstract) (23 Refs)

37. ALKALINE PHOSPHATASE ISOZYMES FROM RAT TRANSPLANTABLE GASTRIC CARCINOMA TISSUES INDUCED BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE (MEETING ABSTRACT).

Miki K, Kobori O, Ichinose M, Miyazaki J, Iino S, Niwa H, Suzuki H, Oka H, Oda T

1st Department of Internal Medicine, University of Tokyo, Tokyo, Japan

Oncodev Biol Med; AbstractsBook,1:P11 1981

Experimental gastric carcinoma was developed in inbred Wistar strain rats by oral administration of N-methyl-N'-nitro-N-nitrosoguanidine, and the resulting tumor was transplanted sc into rats of the same strain. Alkaline phosphatase (ALP) isozymes were determined in these transplantable tumor tissues, and their enzymological and immunological characterizations were analyzed. They did not differ significantly until the 19th generation, and were almost the same as those of primary tumors in out-bred rats; the carcinoma tissues of rat stomach were suspected of producing high amounts of ALP isozymes (major A-band and minor B-band), especially the intestinal-type ALP isozyme (B-band). Therefore, abnormal gene expression in ALP production, especially intestinal-type ALP, seemed to be independent of the strain of rats and inherited in transplantable tumor until the 19th generation. However, after the 20th generation, specific ALP activity gradually decreased and zymogram showed almost only A-band (non-intestinal-type ALP). We propose that experimentally induced rat gastric cancer cells, initially or precancerous condition, produce the A-type of ALP isozyme, finally, as cancer cells develop, they produce the B-type, and ultimately, A plus A-type isozyme appear in the carcinoma tissues. After the 20th generation, ALP isozymes from rat transplantable tumor tissue become similar to ALP isozymes of the precancerous condition. (2 Refs)

38. MNNG INDUCTION OF CANCER IN RESIDUAL STOMACH TISSUE.

Nishitoi H

First Dept. Surgery, Tottori Univ., Tottori, Japan

I To Cho; 16(9):942 1981

N-methyl-N'-nitro-N-nitrosoguanidine (MNNG; 120 ug/ml) and 0.4% Tween 60 were administered in drinking water to male Wistar rats during mo 1-6 following hemigastrectomy, and the rats were sacrificed at mo 8. The rats were divided into four groups, based on type of surgical procedure used: Billroth-II reconstruction, Roux-Y anastomosis, gastric section, and no surgery (controls). Adenocarcinomas (primarily differentiated type) were observed in 7/18 rats subjected to Billroth-II reconstruction, 5/20 subjected to Roux-Y anastomosis, 3/20 subjected gastric section, and 2/21 serving as controls. Cancers were observed in the anastomotic site in the Billroth-II and Rous-Y group rats, in the pyloric region towards the lesser curvature in the gastric section and control rats, and throughout the region of the gastric resection in one of the rats of the gastric section group. Gastric pH of the rats subjected to Billroth-II reconstruction was high (5.1) at the time of sacrifice; those of the Rous-Y and gastric section rats were 4.5 and 2.8, respectively. Reflux of bile from the duodenum was suspected of being implicated in postgastrectomy increases in gastric pH, ulceration of the gastric anastomosis, constricting gastritis, and occurrence of cancer of the residual stomach. (no Refs) (In JPN)

39. EXPERIMENTAL BRAIN TUMORS AND EDEMA IN RATS: I. HISTOLOGY AND CYTOLOGY OF TUMORS.

Hurter T, Mennel HD

Max-Planck Inst. for Brain Res., Ostmerheimer Str. 200, D-5000 Cologne 91, W. Germany

Acta Neuropathol (Berl); 55(2):105-111 1981

Histology and cytology of experimental brain tumors were studied in BD-IX rats. Tumors were induced by stereotactic reimplantation into the left brain hemisphere of cloned cells derived from a methylnitrosourea-induced tumor. After 2-3 wk, tumors had a diameter of 2-3 mm and were characterized by necroses, large vessels, and edema of the left hemisphere. The tumor center was composed primarily of rounded cells with spheroidal nuclei and light cytoplasm. Most of these cells could be s tained by impregnation with silver salts. Peripheral tumor cells were largely bipolar with decreased affinity for specific glial silver stains. Surrounding brain tissue was infiltrated by tumor-cell processes. Central cells had a well-developed Golgi apparatus, sometimes fused with vacuoles resembling lysosomes. Tumor vessels were poorly structured and lacked a glial sheath. Endothelial fenestrations or open tight junctions were not found, indicating that edema was the result of pinocytic transport. The experimental tumors were comparable to low-differentiated human oligodendroglioma. (36 Refs)

40. REGIONAL BLOOD FLOW AND CAPILLARY PERMEABILITY IN THE ETHYLNITROSOUREA-INDUCED RAT GLIOMA.

Yamada K, Hayakawa T, Ushio Y, Arita N, Kato A, Mogami H

Dept. Neurosurgery, Osaka University Medical Sch., 1-1-50, Fukushima, Osaka 553, Japan

J Neurosurg; 55(6):922-928 1981

Regional cerebral blood flow and capillary permeability of rat brains bearing ethylnitrosourea-induced gliomas of various size were investigated with 14C-antipyrine autoradiography and Evans blue staining. In the small tumors (less than 2 mm in diameter), blood flow was uniformly reduced when compared to the adjacent brain. Even in tiny tumors (0.3 to 0.4 mm in diameter), reduction in blood flow was evident. In the medium (2 to 4 mm in diameter) and large (greater than 4 mm in diameter) tumors, the blood flow increased or decreased depending on the part of the tumor examined. The necrotic center and peripheral edge had low blood flows, whereas the viable portion adjacent to the necrotic center had high blood flows. Blood flow in the brain tissue adjacent to medium and large tumors was lower than control brain tissue, probably due to local edema. Leakage of iv Evans blue in the tissue was only evident in the large tumors with central necrosis. The present findings suggest that neovascularization of the tumor may occur when the tumor reaches a certain size, and leaky new vessels may be the cause of brain edema associated with tumor. (Author abstract) (16 Refs)

41. A TRANSPLANTABLE LARGE-CELL LYMPHOBLASTIC LYMPHOMA IN XENOPUS LAEVIS (MEETING ABSTRACT).

Balls M, Clothier R, Knowles K

Department of Human Morphology, University of Nottingham, Nottingham, NG7 2UH, England

Cell Biol Int Rep; 5(SupplA):1 1981

Six mo after the completion of a course of seven, weekly ip injections of 7 mg N-methyl-N-nitrosourea (NMU) per 100g body wt, the normal tissues of the liver, spleen and thymus glands of an adult female Xenopus laevis (the South African

clawed toad) were found to have been largely replaced by lymphoblastic lymphoma cells. Extensive tumor cell infiltration was also found in the kidneys, pancreas, lungs, and below the epithelial lining of the gut. Tumor-containing liver fragments were implanted into the dors al lymph sac of two groups of 10 Xenopus toadlets, whose allograft response capacity had been impaired either by thymectomy during early larval development or by exposure to a single NMU dose. Lymphomas developed in the same range of tissues within 60 days. Four toadlets from each group were given 15mg NMU per 100g body wt 73, 80 and 87 days after tumor implantation. Liver biopsies were taken two days after the first NMU dose, and samples of a range of tissues from these and other tumor-bearing toadlets not given NMU were taken two days after the final NMU dose. Histological examination showed that NMU treatment resulted in lymphoma cell death and tumor regression. A single dose of NMU is selectively lymphocytotoxic in Xenopus; a temporary suppression of humoral and cell-mediated immune responses is followed by lymphoid tissue regeneration but allograft immune competence does not return. Lymphoblastic lymphoma cells in this species appear also to be highly susceptible to damage by NMU. (1 Ref)

42. GENETIC STUDY OF N-NITROSOMETHYLUREA-INDUCED THYMIC LYMPHOMA IN INBRED MICE (MEETING ABSTRACT).

Mayer A
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Mice of various inbred strains were injected ip with the chemical carcinogen N-nitrosomethylurea to induce thymic lymphoma. All the strains developed this specific neoplasia to high incidences, but marked differences were observed between strains with respect to the duration of the latent period, which extended from exposure to the carcinogen at 5-9 wk of age until overt development of thymic lymphoma (indicated by labored breathing) followed shortly thereafter by death. The RF/J and AKR/J strains showed the shortest latent periods, with deaths occurring from 12 to 18 wk of age. The 129 and C57BL/6 strains were characteristic of the longer-latency type, with deaths occurring from 16 to 30 wk of age. In two crosses tested, the AKR x 129 and the 129 X RF, the short-latency phenotype was observed to be dominant. Data from the (129 x RF) F1 x 129 backcross will be presented to indicate the number of loci involved in the short-latency phenotype, and to discern whether endogenous ecotropic murine leukemia virus and/or the H-2 locus plays a role in this phenomenon. (no Refs)

43. HEMOPOIETIC FUNCTIONS DURING THE LATENCY PERIOD OF BNU INDUCED LEUKEMOGENESIS IN MICE (MEETING ABSTRACT).

Seidel HJ, Kreja L
Department of Clinical Physiology and Occupational Medicine, University of Ulm, Oberer Eselsberg, D-7900 Ulm/Donau, W. Germany
Exp Hematol; 9(Suppl9):180 1981

It has been shown that hemopoietic stem cells and various immune functions are depressed in mice during a leukemogeneic butylnitrosourea (BNU) exposure period of 12 wk. This is followed by a latency period of varying length and more than 95% of the animals will die of leukemia. In the present study we looked for transplantable 'preleukemic' cells during and after the BNU exposure and tested colony forming units (CFU-S) and the immune status during the BNU-free interval in groups as well as in individual mice. During the BNU exposure no 'preleukemic' cell could be detected, but later leukemia inducing cells could be transplanted in some mice without clinical signs of leukemia. During the BNU free interval a partial regeneration of CFU-S was seen and a recovery of B and T-cell responses, the MLC however remained below normal control levels. Natural killer cell activities are added at present. The study of a rather large series of individual mice shows that all mice, independent of the presence of detectable leukemic cell in thymus, spleen or bone marrow, have reduced numbers of CFU-S and also in most cases a reduced mixed lymphocyte reactivity. All immunological tests become negative in mice with advanced leukemia and CFU-S fall to very low levels. In summary, many the deficiencies seen during the BNU exposure are at least in part reversible and may just reflect toxicity. Mice studied in the BNU free interval are characterized by reduced numbers of CFU-S and a depressed MLC reactivity. (1 Ref)

MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS

44. INHIBITORY EFFECT OF 4,4'-DIAMINODIPHENYLMETHANE ON LIVER, KIDNEY AND BLADDER CARCINOGENESIS IN RATS INGESTING N-ETHYL-N-HYDROXYETHYLNITROSAMINE OR N-BUTYL-N-(4-HYDROXYBUTYL)NITROSAMINE.

Fukushima S, Hirose M, Hagiwara A, Hasegawa R, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Carcinogenesis; 2(10):1033-1037 1981

Effects of 4,4'-diaminodiphenylmethane (DDPM) in the 'post-initiation' stage of liver, kidney, and bladder carcinogenesis induced in male F344 rats by N-ethyl-N-hydroxyethylnitrosamine (EHEN) or by N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) were investigated. Rats given 0.1% EHEN in drinking water for 2 wk followed by DDPM treatment (0.1% in diet, 32 wk) had significantly fewer renal neoplastic nodules (av 0.28/cm2) and renal cell tumors (av 0.16/cm2) than rats treated with EHEN alone (1.88 neoplastic nodules and 0.51 renal cell tumors/cm2). DDPM did not inhibit development of hyperplastic nodules in the liver. However, hepatocellular carcinomas did not occur in rats treated with EHEN and DDPM, whereas they were observed in 7/21 rats treated with EHEN alone. DDPM (0.1% in diet, 34 wk) also reduced the frequency of bladder papillomas induced by 4 wk or BBN treatment (0.01% in drinking water). In these experiments, rats treated with DDPM showed growth retardation and decreased food intake. (25 Refs)

45. INHIBITION OF DENA-LIVER CARCINOGENESIS IN RATS WITH SODIUM OXYFERRISCORBONE.

Blagoeva PM, Balanski RM
Oncological Res. Inst., Medical Acad., Sofia, Bulgaria
Dokl Bolg Akad Nauk; 34(5):711-712 1981

Hepatocarcinogenesis induced in male BD/6 rats by nine weekly ip injections of diethylnitrosamine (80 mg/kg body wt) was reduced by 33% when animals were treated with a prophylactic regimen of sodium oxyferriscorbone (2 mg/kg body wt, ip five times per wk for 5 mo). It is suggested that sodium

oxyferriscorbone may interfere with the oxidation-reduction processes in target tissues. (12 Refs)

46. COMPARISON OF HEPATIC CARCINOGEN INITIATION-PROMOTION SYSTEM (MEETING ABSTRACT).

Leonard TB, Dent JG, Graichen ME, Popp JA
Chemistry Industrial Institute Toxicology, Research Triangle Park, NC, 27709
Toxicologist; 1(1):154 1981

A number of model systems have been designed to study the initiating and promoting phases of neoplastic development in rat liver. The purpose of these experiments was to determine if the promoting protocols alone altered liver biochemistry. Four protocols, which use the same initiator, diethylnitrosamine (DEN), but different promotional regimens, were investigated. The biochemical parameters evaluated were hepatic microsomal benzphetamine-N-demethylase (BPND), epoxide hydratase (EH), cytosolic DT-diaphorase, serum glutamic pyruvic transaminase (GPT) and serum gamma glutamyl transpeptidase (GGT) activities. The effect of initiation in these protocols was also evaluated to ascertain if DEN caused changes in liver biochemistry and if these changes were related to preneoplastic lesions. All 4 promoting regimes depressed BPND (20-50% of control) and all except one increased EH and DTD (3-fold). SGGT was elevated by all protocols (10x) but SGPT was only slightly changed. The combination of DEN initiation with promotion increased hepatic GGT positive foci (identified histochemically) but did not alter the biochemical parameters studied. We conclude that measurement of these enzymes is of no value for predicting neoplastic change. However, the data show that liver biochemistry, especially with respect to drug metabolism, is extensively altered by the promotional regimes. Consequently, study of promoter-induced changes in drug metabolizing enzymes may lead to a better understanding of biochemical events during promotion in hepatocarcinogenesis. (4 Refs)

47. INITIATION/PROMOTION ASSAY FOR CHEMICAL CARCINOGENS IN RAT LIVER (MEETING ABSTRACT).

Pereira MA, Herren SL, Britt AL, Khoury M
Health Effects Research Laboratory, US Environmental Protection Agency, Cincinnati, OH, 45268
Toxicologist; 1(1):155 1981

We have developed a short-term initiation/promotion assay in rat liver for the detection of chemical carcinogens. Male rats (175-200 gm) were po administered the chemical under test. One wk later tumor promotion by 500 ppm sodium phenobarbital in the drinking water was commenced. A fter 8 wk of promotion the rats were sacrificed and the liver stained and scored for gamma glutamyl transpeptidase (GGTase) positive foci. The appearance of GGTase positive foci was taken as an indication of the initiation of carcinogenesis by the chemical. In some cases partial hepatectomy was performed 24 hr prior to the administration of the test chemical in an attempt to increase the sensitivity of the assay. Acetylaminofluorene (AAF), aflatoxin B1 (AFB1) benzo(a)pyrene (BaP), diethylnitrosamine (DENA), 7,12-dimethylbenzo(a)anthracene (DMBA), dimethylnitrosamine (DMNA), N-methyl-N'-nitro-N-nitrosoguaninidine and urethane were positive in the assay while benzene (30 mmole/kg) was apparently negative. Phenobarbital promoted the response of AAF, AFB, DENA, DMBA and DMNA. Partial hepatectomy 24 hr prior to initiation increased the response of AAF, BaP, DENA and DMBA. The initiation/promotion assay in rat liver that includes 1) partial hepatectomy at 24 hr prior to administering the test chemical, 2) phenobarbital promotion and 3) GGTase foci as indication of carcinogenic activity; would appear to be sensitive to a wide variety of chemical carcinogens. (no Refs)

48. INFLUENCE OF PROLACTIN AND GROWTH HORMONE ON RAT MAMMARY TUMORS INDUCED BY N-NITROSOMETHYLUREA.

Rose DP, Noonan JJ
Div. Clinical Oncology, Wisconsin Clinical Cancer Center, Univ. Wisconsin, Madison, WI, 53792
Cancer Res; 42(1):35-38 1982

The effects of hypophysectomy and prolactin-suppressing drugs on the growth of mammary tumors induced in Sprague-Dawley rats by N-nitrosomethylurea and dimethylbenz(a)anthracene were compared. The influence of ovine prolactin and growth hormone administration on N-nitrosomethylurea-induced tumors was also studied in hypophysectomized animals. After hypophysectomy, all 13 tumors induced in 13 rats by N-nitrosomethylurea underwent regression, as did 10 of 12 induced by dimethylbenz(a)anthracene. There were no new tumors. Pergolide mesylate, a long-acting ergoline derivative, was given in a dose of 80 ug bid by sc injection for 28 days. Only 3 of 12 N-nitrosomethylurea-induced tumors regressed, while 4 became static. However, only two new tumors developed in the 12 pergolide-treated rats, compared to 11 in the 12 untreated controls. Bromocriptine mesylate, at 10x the pergolide dose, was even less effective; one of 16 tumors regressed, 2 became static, and 8 new tumors appeared in the 16 rats. In contrast, 8 of 12 dimethylbenz(a)anthracene-induced tumors regressed during pergolide therapy, 2 became static, and there was only 1 new tumor among the 12 rats. Prolactin, 1 mg bid for 7 days by sc injection, was given to another eight rats bearing 11 N-nitrosomethylurea-induced tumors, commencing 7 days after hypophysectomy. Regression of five tumors borne by four rats was reversed but resumed when treatment was st opped. Regression of five tumors in the other four animals was arrested without regrowth; the sixth became impalpable. All of these six grew rapidly when growth hormone, 2 mg bid, was administered in addition to prolactin. (Author abstract) (21 Refs)

49. ACTIVITY OF THE ANTIOESTROGEN TRIOXIFENE AGAINST N-NITROSOMETHYLUREA-INDUCED RAT MAMMARY CARCINOMAS.

Rose DP, Fischer AH, Jordan VC
Div. Clinical Oncology, Wisconsin Clinical Cancer Center, Univ. Wisconsin, Madison, WI, 53792
Eur J Cancer Clin Oncol; 17(8):895-898 1981

The therapeutic efficacy of a new antiestrogen, trioxifene, was compared with that of tamoxifen and ovariectomy against rat mammary tumors induced by N-nitrosomethylurea. In control animals, all but 1/59 tumors either progressed (52) or remained static (6) and 31 new tumors appeared. All three modes of therapy were highly effective. Trioxifene mesylate, (300 ug sc daily) induced regressions in 26/61 (42.6%) tumors, and stasis in 13 (21.3%). Nine new tumors appeared during trioxifene treatment. Tamoxifen (200 ug sc daily), produced regression of 22/50 tumors (44.0%), while 19 (38.0%) remained static and 2 new tumors developed. Ovariectomy caused regression of 35/56 (62.5%) tumors, growth was inhibited in another 8 (14.3%) and 2 new tumors developed. Regression after ovariectomy was greater compared with trioxifene therapy (p less than 0.04), but no different for ovariectomy and tamoxifen, or

tamoxifen and trioxifene. The relative binding affinity (RBA, OE2 = 100) of trioxifene (8.8-11) for NMU-induced mammary tumor estrogen receptors was consistently 4-5x greater than that of tamoxifen. The comparative study in vitro did not parallel the finding in vivo. However, the RBA of monohydroxytamoxifen, a metabolite of tamoxifen, was the same or 2x greater than that of estradiol, suggesting that tamoxifen's action may be facilitated by conversion to active metabolites. Further study of trioxifene's metabolites may increase our understanding of its mechanism of action in vivo. (Author abstract) (17 Refs)

50. EFFECTS OF THE INTERACTION OF DIETARY FAT AND PROTEIN ON EXPERIMENTAL PANCREATIC CANCER IN SYRIAN HAMSTERS (MEETING ABSTRACT).

Birt DF, Pour PM
Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, NE, 68105
Newsletter Natl Pancreas Cancer Project; VI(2):10 1981

The effects of dietary protein on pancreatic carcinogenesis by N-nitrosobis-(2-oxopropyl)amine (BOP) in the Syrian hamster were evaluated at three dietary fat levels. In previous reports we demonstrated enhanced pancreatic ductular carcinoma yield as the dietary fat level rose. Syrian hamsters were fed three levels of dietary protein (P) as casein [9 low (LP), 18 medium (MP) and 36 high (HP) g/385 Kcal] with each of three levels of fat (F) as corn oil [4.5 low (LF), 9.0 medium (MF) and 18.0 high (HF) g/385 Kcal] either before (3-7 wk of age) or after (8 wk-death) treatment with a single injection (10 mg/kg sc) of BOP. Carcinoma yields were modified by diet only in hamsters fed the various diets after BOP administration. The enhanced carcinoma yield with increasing fat intake after BOP as observed at the MP level was also seen at the HP level in both sexes [HP-LF, 7/47 (15% incidence); HP-HF, 19/55 (35% incidence)]. Effects of dietary protein on carcinoma incidence were observed at the MF level in females [LP-MF, 0/28 (0%); HP-MF, 8/27 (30%)], but not in males [LP-MF, 10/29 (34%); HP-MF, 5/24 (21%)]. In hamsters fed the HF diets the lowest protein level resulted in a decrease in carcinoma yield [LP-HF, 1.5 carcinomas/total body area (TBA); HP-HF, 3.6 carcinomas/TBA]. Pancreatic adenomas were influenced by dietary fat and protein levels before or after BOP treatment. Feeding the low protein diets dramatically reduced adenoma yield, particularly at the high fat level. For example, feeding LP-HF and HP-HF diets to male hamsters resulted in 8 and 14 adenomas/TBA respectively when fed before BOP and 15 and 31 adenomas/TBA when fed after BOP. (no Refs)

51. OPERATION-SEQUEL CARCINOMA OF THE STOMACH. EXPERIMENTAL STUDIES OF SURGICAL TECHNIQUES WITH OR WITHOUT RESECTION.

Langhans P, Heger RA, Hohenstein J, Schlake W, Bunte H
Chirurgische Universitatsklinik, Jungeblodtplatz 1, D-4400 Munster, W. Germany
World J Surg; 5(4):595-605 1981

Groups of female Wistar rats were studied to determine the role of surgical trauma, duodenogastric reflux, and carcinogen administration in development of gastric carcinoma. The rats underwent one of the following procedures: Billroth I resection, Billroth II resection, Billroth II resection with Roux-en-Y gastroenterostomy, Billroth II resection with Braun's anastomosis, gastroenterostomy without resection, or no operation. Each group was divided onto two subgroups, one receiving N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) for 7 mo (av dose 6.9 mg/day) and the other receiving no carcinogen. Autopsy was performed 56 wk after surgery in a total of 209 surviving animals. The results indicated that surgical trauma alone did not influence the incidence of gastric tumors. However, tumor incidence rose in parallel with intensity of duodenogastric reflux. No tumors occurred in any of the carcinogen-treated or untreated rats that had undergone Billroth II resection with Roux-en-Y gastroenterostomy, a procedure which produces no reflux. Tumor incidence rose to 13.6% in MNNG-treated rats that had received Billroth I resection and to 10% in untreated rats undergoing the same procedure. Carcinogen-treated and untreated animals receiving Billroth II resection with Braun's anastomosis had tumor incidence of 16.7% and 23.1%, respectively; those with Billroth II resection alone had incidence of 38.9% and 30%, respectively. The highest incide nce occurred in rats subjected to gastroenterostomy alone (50% with and 70.8% without MNNG treatment). Among the 29 animals with duodenogastric fistulae, 25 (14/15 carcinogen-treated and 11/14 untreated) eventually developed carcinomas in the gastric part of the fistula. The carcinogenic potential of MNNG appeared markedly lower than that of duodenogastric reflux provoked by resection. Results support the hypothesis that biliary reflux favors development of gastric malignancy; techniques for gastric resection which eliminate reflux are evidently superior.. (11 Refs)

52. UREIDO-ETHYL-IMIDAZOLINES ACTIVE AGAINST AUTOCHTHONOUS DIETHYLNITROSAMINE-INDUCED EPIDERMOID, PAPILLARY AND ADENOCARCINOMATOUS TUMORS OF THE RESPIRATORY TRACT OF SYRIAN HAMSTERS AND AGAINST HUMAN BRONCHOGENIC CARCINOMAS IN NU/NU MICE.

Marxer A, Schmidt-Ruppin KH
Chemical and Biological Res. Lab., Pharmaceuticals Div. CIBA-GEIGY Ltd., CH-4002 Basel, Switzerland
Experientia; 37(11):1123-1131 1981

The detection of a new class of tumor inhibiting substances is described. Employing a chemical reaction discovered several yr ago, a series of imidazolinylureas were prepared. It was found that some compounds of this group were active against diethylnitrosamine (DENA)-induced tumors in hamsters. CGP 15720 A (1- *2-[2-(4-pyridyl)-2-imidazole-1-yl]-ethyl* -3-(4 carboxy-phenyl)urea), the most active compound at present, was developed through a series of structural variations. CGP 15720 A inhibits significantly in oral or parenteral treatment with well tolerated doses (10-30 mg/kg) the progressive growth of autochthonous, DENA-induced papillary, epidermoid and adenocarcinomatous tumors of the respiratory system in Syrian hamsters and prolongs significantly the survival. The substance also inhibits significantly the growth of two poorly differentiated human epidermoid or anaplastic bronchogenic carcinomas in nu/nu Balb/c mice and prolongs the mean survival time. In these mice, the substance is also active against the rodent ascites tumors Ehrlich carcinoma, CrSa 180 and Yoshida Sa AH 66, although it is only marginally active or inactive against these tumors in normal mice or rats. In the therapeutic trials, hamsters tolerated the highest dose administered for 4 wk, 1,000 mg/kg po, without signs or symptoms of toxicity. (Author abstract) (35 Refs)

53. INHIBITION OF THE CARCINOGENIC EFFECT OF NITROSOMORPHOLINE FORMED IN VIVO.

Borzsonyi M, Torok G, Pinter A, Surjan A, Csik M, Bar V
Orszagos Kozegeszsegugyi Intezet, Budapest, Hungary
Egeszsegtudomany; 25(3):248-250 1981

The effect of 6,6'-methylene-bis-2,2-dimethyl-4-methanesulfonic acid sodium salt of 1,2-dihydroquinoline (MTDQ-DA) on lung adenoma induction of nitrosomorpholine formed in vivo from morpholine and sodium nitrite administered intragastrically (ig) was studied in 4-5-wk-old female CFLP mice. T he animals were killed 8 mo after the treatment. The number of lung adenomas per tumor-bearing mouse was 0.13 in the untreated controls, 0.11 in controls treated with 500 mg/kg MTDQ-DA ig, 0.14 in controls treated with morpholine only (1,000 mg/kg), 16.58 in a group treated with morpholine (1,000 mg/kg), plus sodium nitrite (125 mg/kg ig); 2.47 in another group treated with MTDQ-DA (500 mg/kg ig), morpholine (1,000 mg/kg), and sodium nitrite (125 mg/kg), 0.21 in another group treated with sodium nitrite only (125 mg/kg), and 0.17 in a control group treated with MTDQ-DA (500 mg/kg) plus sodium nitrite (125 mg/kg). The exact mechanism of the nitrosation-inhibiting action of MTDQ-DA is unknown: it may rapidly react with the nitrite, C-nitrosation may take place, or nontoxic and noncarcinogenic N-nitroso compound may be formed. (20 Refs) (In HUN)

54. INFLUENCE OF NITROGEN DIOXIDE OR FORMALDEHYDE ON INCIDENCE OF DIETHYLNITROSAMINE-INDUCED TUMORS IN HAMSTER RESPIRATORY TRACT (MEETING ABSTRACT).

Dalbey W, Nettesheim P
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN
Toxicologist; 1(1):138 1981

The potential enhancing activity of two model irritant gases, nitrogen dioxide and formaldehyde, on chemically induced tumors in the respiratory tract was investigated. Adenomas were produced throughout the respiratory tract of male Syrian golden hamsters by 10 weekly sc injections of 0.5 mg of diethylnitrosamine (DEN). Hamsters also received weekly 5-hr exposures to either nitrogen dioxide (10 ppm) or formaldehyde (30 ppm). Gas exposures were begun either concurrently with DEN (a single exposure 48 hr prior to each DEN injection) or two wk after the last DEN injection. Gas exposures continued for lifetime. DEN treatment increased mortality above that of untreated controls; formaldehyde exposures of DEN-treated hamsters increased mortality further. Tumor incidence was evaluated on a subgross level after staining and clearing of whole organs of the respiratory tract. Histologic sampling of observed lesions verified this method of scoring tumors. The number of tumor bearing animals (TBA) was not increased by irritant gas exposures of DEN-treated hamsters, but the number of tumors per TBA was significantly increased by exposure to formaldehyde concurrent to DEN treatments. (no Refs)

55. EFFECTS OF RAT URINE FRACTIONATED BY MOLECULAR WEIGHT ON URINARY BLADDER CARCINOGENESIS.

Babaya K, Miyata Y, Chmiel JS, Oyasu R
(c/o Oyasu) Dept. Pathology, Northwestern Univ. Medical Sch., Chicago, IL, 60611
Cancer Res; 42(1):15-18 1982

Experimental evidence suggests that rat urine plays a dual role in urinary bladder carcinogenesis, as a carrier of carcinogen(s) and an enhancer (or promoter) of carcinogenesis in carcinogen-initiated cells. The present experiment was conducted to determine whether -tumor-enhancing activity exhibited by the whole urine resides in a specific fraction(s) when separated by mol wt. Normal rat urine after preliminary filtration to remove gross debris was filtered through Amicon Diaflo membranes to obtain two types of filtrate, one at an exclusion level of mol wt 1,000 and the second at an exclusion level of mol wt 50,000. These filtrates were tested for tumor-enhancing activity in the heterotopically transplanted rat urinary bladders (HTBs) removed from rats pretreated with the carcinogen N-butyl-N-(4-hydroxybutyl)nitrosamine in drinking water for 4 or 10 wk. the incidences of cancer in HTBs receiving repeated instillations of the filtrate at mol wt 50,000 did not differ significantly from those of the HTBs receiving whole urine but were significantly higher than those of the HTBs receiving the filtrate at mol wt 1,000. In the HTBs, which had been exposed to the carcinogen for a longer period of time (10 wk), the filtrate at mol wt 1,000, enhanced the bladder tumorigenesis over that of the osmolality control. The results indicate that there may be two classes of tumor-enhancing activity: the first and major one being in the fraction above mol wt 1,000; and a second one being below mol wt 1,000. the latter fraction appears to exert its effects only on the cells which are in an advanced stage of carcinogenesis. (Author abstract) (10 Refs)

56. TUMOR PROMOTION IN RAT LIVER (MEETING ABSTRACT).

Herren SL, Pereira MA
U.S. Environmental Protection Agency, Cincinnati, OH
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

An initiation/promotion bioassay using gamma glutamyl transpeptidase (GGTase) positive foci as the endpoint has been developed that can detect the carcinogenic potential of chemical carcinogens. GGTase-positive foci are presumed to be areas of initiated hepatocytes in contrast to the GGTase-positive areas of Zone 1 diffusion observed with compounds such as phenobarbital and saccharin. To evaluate the tumor promoting activity of phenobarbital, rats were administered diethylnitrosamine (DENA), 0.3 mmole/kg, followed by 500 ppm phenobarbital in their drinking water. After six wk of phenobarbital promotion, the rats had an increased incidence of foci as compared to non-phenobarbital treated rats. By 50 wk of phenobarbital promotion, the number of foci in the non-promoted animals equaled the number observed with promotion. This demonstrated that the initiator determined the ultimate number of foci while the promoter decreased the latent period required for the observation of foci. In an experiment to determine the effect of phenobarbital on the stability and progression of GGTase-positive foci, rats received a 2/3 partial hepatectomy, followed 24 hr later by DENA (0.3 mmole/kg). The rats then received 500 ppm phenobarbital in the drinking water for eight wk. After eight wk, half of the rats were continued on phenobarbital and the other half were taken off phenobarbital. The number of foci/cm 2 observed in rats continued on phenobarbital treatment leveled off after 10 wk of continuous promotion approached that observed with continuous phenobarbital promotion, while the number of foci/cm2 in the rats taken off phenobarbital initially decreased. However, 56 wk after the administration of DENA, the number of foci/cm2 from the rats removed from phenobarbital promotion approached that observed with continuous phenobarbital promotion, although the size of the foci from the rats on continuous promotion was larger. After 81 wk, all six (100%) of the rats on continuous

promotion had liver tumors while only three of six (50%) rats removed from promotion had tumors. Therefore, continuous promotion by phenobarbital not only decreased the latent period for the appearance of foci, but also increased the size of DENA initiated foci as well as ultimately increasing the incidence of liver tumors. (no Refs)

57. COMPARISON OF VARIOUS PROMOTING AGENTS ON THE INDUCTION OF PRENEOPLASTIC LESIONS IN THE RAT LIVER (MEETING ABSTRACT).

Ito N, Tsuda H, Hasegawa R, Imaida K
Nagoya City University Medical School, Nagoya 467, Japan
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Rats were injected ip with N-nitrosodiethylamine (DEN) or saline (control) as an initiator. Two wk after this, rats were given test compounds mixed in the basal diet or drinking water for six wk and then killed. The results show that administration of strong hepatocarcinogens such as aflatoxin B1, DEN, N-nitrosodimethylamine (DMN), 2-acetylaminofluorene (2-AAF), 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB), thioacetamide, sterigmatocystin and ethionine resulted in large numbers of hyperplastic (neoplastic) liver nodules, whereas, dieldrin, dichloro-diphenyl trichloroethane (DDT), polychlorinated biphenyls, and alpha-hexachlorocyclohexane had less promoting effects. Non-hepatocarcinogens, such as N-nitrosoethylurea and 3-methylcholanthrene, also slightly enhanced the induction of hyperplastic nodules. Of the miscellaneous compounds tested, phenobarbital, deoxycholic acid and ethinyl estradiol enhanced the nodule induction. Hepatocarcinogens and chemic[illegible] with promoting activity in liver carcinogenesis gave positive results in this system. Thus our system could be used for screening hepatocarcinogens or hepatopromoters and also estimating their potency. (no Refs)

58. QUANTITATIVE STUDIES OF EARLY STAGES IN MOUSE HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Goldfarb S, Pugh TD, Koen H, Vesselinovitch SD
University of Wisconsin, Madison, WI
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

We previously reported that single ip injections of diethylnitrosamine (5 ug per g body wt) in 15-day-old male B6C3 F1 mice caused the early induction of foci of RNA-rich hepatocytes that lacked glucose-6-phosphatase activity, showed high rates of cell replication, and had a strong tendency to invade terminal hepatic veins. The foci showed features of tumor progression including a doubling of tritiated thymidine labeling indices between 20 to 28 wk and the development at 44 wk into typical trabecular hepatocellular carcinomas. Recently, we carried out serial section reconstructions of over 700 foci in a total of 17 livers from mice killed at 10, 20 and 28 wk. Foci were assigned to one of nine different log incremental size classes with equatorial plane areas between .005 to 2.5 mm2. The av number of foci per liver was 313 at 10 wk, 938 at 20 wk, and 1,050 at 28 wk. Because the foci were close to spherical in shape and increased in number, we believe that regression or remodeling did not occur. Despite a slowing down in the rate of emergence of the foci, their aggregate tumor vol continued to increase logarithmically through 36 wk of study. A method using smoothing splines and developed in collaboration with statisticians at the University of Wisconsin accurately estimated the number and size distribution of foci. The unequivocal identification of malignant and premalignant lesions in solid organs and the accurate quantitation of their number, size, and growth rates, should greatly facilitate the determination of potency of initiators and promoters of carcinogenesis. (1 Ref)

59. CHEMICAL LIVER CARCINOGENESIS, MONITORING OF THE PROCESS BY FLOW CYTOMETRIC DNA-MEASUREMENTS (MEETING ABSTRACT).

Digernes V
Institute of Pathology, Oslo 1, Norway
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

The carcinogenic process in the liver was monitored from early non-neoplastic changes to the development of tumors in two well known models; giving Dimethylnitrosamine (DMN) ip to newborn mice, and feeding rats with Acetylaminofluorene (AAF). Liver parenchyma cells and liver tumor cells were isolated by collagenase treatment and prepared for flow cytometric (FCM) measurements of nuclear DNA content. The changes observed were correlated to morphology and 3H-thymidine incorporation. The early preneoplastic changes in hepatocytes from DMN-treated mice were shifts in the DNA content to classes of higher nuclear ploidies. AAF-feeding of rats caused gradual distortion of the DNA content of nuclei from parenchymal cel ls. After 16 wk of exposure, before any tumors were seen, a majority of the nuclei displayed an aneuploid DNA content. The significance of these changes in the carcinogenic process is discussed, and a possible use of these models for detection of hepatotrophic agents and agents causing aneuploidy (clastogens and turbagens) is proposed. The liver neoplasias (adenomas and hepatocellular carcinomas) induced by these models contained tumor stemlines with diploid DNA content, some hepatocellular carcinomas showed aneuploidy. Proliferative nodules contained diploid and tetraploid stemlines. (no Refs)

60. ORAL CONTRACEPTIVE STEROIDS AS PROMOTERS AND COMPLETE CARCINOGENS FOR LIVER IN FEMALE SPRAGUE DAWLEY RATS (MEETING ABSTRACT).

Yager JD
New York University Medical School, New York, NY
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Recent reports have described an increased incidence of adenomas and hepatocellular carcinomas in livers of women with a history of long-term oral contraceptive use. Evidence derived from human and experimental animal data suggests that oral contraceptive steroids may be liver tumor promoters. Studies being carried out in my laboratory were designed to determine whether two oral contraceptive steroids, mestranol and norethynodrel, can promote diethylnitrosamine (DEN)-initiated hepatocarcinogenesis. Studies have also been conducted to determine whether these agents exhibit any detectable genotoxic effects on liver cells which would indicate that they are capable of initiating hepatocarcinogenesis. In the studies designed to detect the promoting potential of these agents, female Sprague-Dawley rats were partially hepatectomized and treated with DEN 24 hr later to initiate hepatocarcinogenesis. Twenty-four hr after injection the animals were transferred to

diet containing the agent to be tested. In two separate experiments, animals were killed after 4, 9 and 12 mo of feeding diets containing the oral contraceptive steroids. Both intact animals and hepatocytes in primary culture were employed in studies designed to detect the ability of the oral contraceptive steroids to cause genetic damage in liver cells. Genotoxicity was assessed by using techniques to detect DNA damage either directly or indirectly. The results from all of these studies indicate the following: 1) mestranol and norethynodrel can promote DEN-initiated hepatocarcinogenesis as indicated by increased numbers of gamma-glutamyl transpeptidase positive, putative preneoplastic lesions after 4 and 9 mo and possibly adenomas and carcinomas after 12 mo; 2) mestranol appears to cause alterations in DNA as detected using alkaline elution; however, this is not reflected by the occurrence of detectable levels o f DNA repair. (1 Ref)

61. COCARCINOGENICITY BY SACCHARIN OF HEPATOCARCINOGENICITY (MEETING ABSTRACT).

Pereira MA
U.S. Enivronmental Protection Agency, Cincinnati, OH
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

We have demonstrated that sodium saccharin was cocarcinogenic towards dibutylnitrosamine (DBN) hepatocarcinogenesis. The simultaneous administration of 5% sodium saccharin in the diet and 0.02% DBN in the drinking water of male rats for 26 wk resulted in a significant increased incidence of preneoplastic foci, hyperplastic nodules and hepatocellular carcinomas compared to rats that received only DBN. The liver of the rats receiving both DBN and saccharin also had an increased incidence of gammaglutamyltranspeptidase (GGTase) positive foci after 4, 8 and 26 wk of treatment. The size distribution of the GGTase-positive foci was the same in the livers of the DBN and DBN-saccharin groups. The livers from rats that only received saccharin did not contain GGTase-positive foci but rather contained at 4 to 8 but not 26 wk a large number of GGTase-positive hepatocytes in Zone 1. It would appear that by 26 wk of saccharin treatment the liver may have developed resistance to saccharin. Our results indicate that the mechanism for the cocarcinogenic activity of saccharin involves an increase in the amount of initiated GGTase-positive foci, and by implication initiation sites of carcinogenesis rather than an increased growth rate of GGTase-positive foci. This implies that the cocarcinogenic activity of saccharin in the liver involves a mechanism different from tumor promoters which act to increase the rate of progression (growth) from the initiated cell to the appearance of cancer. (no Refs)

62. THE EFFECT OF PROMOTERS ON BLADDER CANCER INCIDENCE IN EXPERIMENTAL ANIMAL MODELS (MEETING ABSTRACT).

Hicks RM
Middlesex Hospital Medical School, London, England
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Multistage models of carcinogenesis have been proposed to account for the observed patterns of tumor development in the skin, liver, lung, bladder and other organs. Such models involve initiation of neoplastic change in a few cells by a threshold dose of carcinogen, followed by conversion of these latent tumor cells into an autonomous cancer by further doses of the same and/or other carcinogens, and/or non-carcinogenic promoting agents. In the rat urinary bladder neoplastic change can be initiated by a few wk treatment with low doses of N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) or N-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide (FANFT) or by a single, low dose, intravesicular instillation of N-methyl-N-nitrosourea (MNU). Very few of the animals treated in such a way will develop bladder cancer in their natural life span unless, in addition, they are exposed subsequently to some further regime which will promote tumor growth from the initiated tumor cells. Many different factors will promote tumor growth in the initiated rat bladder including further low doses of complete bladder carcinogens, some dietary factors such as metabolites of tryptophan or deficiency of vitamin A, the food additives saccharin and cyclamate, and some alkylating agents such as cyclophosphamide and methylmethanesulphonate. Although promoters do not necessarily have all the attributes of complete carcinogens, and may not be mutagenic, by accelerating the process of tumor development and thus lowering the age-related cancer incidence in any particular population they may be of prime importance in regulating overall cancer statistics. (no Refs)

63. PROMOTION IN URINARY BLADDER CARCINOGENESIS (MEETING ABSTRACT).

Cohen SM
University of Nebraska College of Medicine, Omaha, NE
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Aromatic amines, including, 2-naphthylamine, 4-aminobiphenyl, and benzidine, are known urinary bladder carcinogens in man and other species, but in rodents, aromatic amines and amides have usually induced liver tumors, occasionally also with tumors of the bladder and other tissues. Variations in organ spicificity are related to differences in metabolism; for bladder the rates of acetylation and deacetylation appear to be critical. Bladder specific carcinogens in rodents and other species have subsequently been identified, including N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) administered in the drinking water, N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (FANFT) in the diet and N-methyl-N-nitrosourea (MNU) instilled intravesically. When low doses of several baldder carcinogens (BBN, FANFT, 2-acetylaminofluorene, and 3,3'-dichlorobenzidine) are administered to rats, either simultaneously or sequentially, a synergistic effect is observed with respect to bladder carcinogenesis. In addition, multistage carcinogenesis has been demonstrated in rats for the bladder using MNU or FANFT as initiators, and sodium saccharin, sodium cyclamate, or tryptophan in the diet as promoters. The urothelium normally has a very low mitotic rate. If mucosal proliferation is increased, such as during fetal development or during regeneration and repair of an ulcer, the bladder appears to be considerably more sensitive to the effects of promoting substances. For example, if sodium saccharin is administered to rats after ulceration of the bla dder, even without prior administration of an initiator, bladder carcinoma develops. Under these conditions, the substance appears as a carcinogen. Human populations with increased bladder epithelial proliferation, such as the fetus, infants, patients with bacterial cystitis, or men with partially obstructive prostatism, may have increased susceptibility to the action of carcinogenic or promoting stimuli. (no Refs)

64. EFFECTS OF PROMOTERS ON N-BUTYL-N-(4-HYDROXYBUTYL) NITROSAMINE INDUCED BLADDER CARCINOGENESIS IN THE RAT (MEETING ABSTRACT).

Ito N

Nagoya City University Medical School, Nagoya 467, Japan

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Male F344 rats were initially given 0.01% N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) for 4 wk in drinking water followed by the feeding of diet containing various chemicals for 32 or 34 wk. In the groups of animals subjected to sodium saccharin, sodium ascorbate, D,L-tryptophan and allopurinol, there was a significant increase in the incidence and number of papillary or nodular hyperplasias (PNH) compared to the groups given BBN alone. However, these compounds did not enhance the induction of papillomas which were generally considered to be more advanced lesions. Experiments were done to determine whether treatment with sodium saccharin or phenobarbital could enhance the neoplastic lesions in the bladder or liver of rats pretreated with 2-acetylaminofluorene (2-AAF) or BBN for initiation. Male Fischer 344 rats were given 0.05% phenobarbital and 5.0% sodium saccharin, respectively for 32 wk after 4 wk administration of hepatocarcinogenesis. Sodium saccharin significantly enhanced the induction of PHN in the bladder, but not of papillomas after BBN treatment, and significantly induced bladder hyperplasias after 2-AAF treatment. However, after 2-AAF or BBN treatment, an effect of phenobarbital for bladder and of sodium saccharin for liver neoplasia induction was not observed. The data indicate that although 2-AAF and BBN have tumor-initiating effects in both liver and urinary bladder, the tumor-promoting effects of phenobarbital and sodium saccharin are organ specific. (no Refs)

65. TUMOR PROMOTERS AND COCARCINOGENS IN TOBACCO CARCINOGENESIS (MEETING ABSTRACT).

Hoffmann D, Hecht SS, Wynder EL

American Health Foundation, Valhalla, NY

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Cigarette smoke induces carcinoma of the larynx in Syrian golden hamsters and is active as a tumor promoter in hamsters pretreated with a low dose of a polynuclear aromatic hydrocarbon, ni trosamine, or nitrosamide. These tumorigenic effects are only observed with total smoke, but not with the gas phase alone. This demonstrates that the tumorigenic agents reside primarily in the particulate phase. According to fractionation experiments, a number of four- and five- ring aromatic hydrocarbons serve as the major tumor initiators in tobacco smoke. Tumor promoters reside primarily in weakly polaric neutral subfractions and in the weakly acidic portion of the particulate matter and include certain unsaturated hydrocarbons and phenolic compounds. Cocarcinogenic activity is a characteristic feature of tobacco smoke and its particulates. Among the cocarcinogens formed during combustion are catechols and certain non-tumorigenic aromatic hydrocarbons and terpenes. Nicotine may also serve as a cocarcinogen as is indicated by preliminary data. The presentation will discuss the action of tumor promoters and cocarcinogens in tobacco carcinogenesis, the precursors for tobacco smoke promoters and cocarcinogens, and methods for their reduction in smoke. (no Refs)

66. TUMOR PROMOTION STUDIES IN RAT TRACHEAL EPITHELIUM (MEETING ABSTRACT).

Steele VE

National Institute of Environmental Health Sciences, Research Triangle Park, NC

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Tracheal epithelium of the Fisher 344 rat is histologically very similar to that of the human bronchus. Also, carcinomas of tracheal origin in F-344 rats are similar in morphology to human bronchogenic carcinomas. Two model systems exist to study tumor promotion in rat tracheal epithelium. The first is a heterotopic tracheal transplant system in which rat tracheas are implanted sc on the backs of isogenic recipients. The epithelium was then topically exposed to pellets containing 7,12-dimethyl-benz(a)anthracene, DMBA, used as the initiating agent, followed by pellets containing the phorbol ester 12-O-tetradecanoylphorbol-13-acetate, TPA, the promoting agent. After 98 wk, 3-4 fold increase in the percentage of tracheas having malignant tumors was seen in tracheal transplants receiving both DMBA and TPA compared to DMBA alone. Exposure of the tracheal grafts to TPA alone resulted in epithelial hyperplasia and inflammation, but no dysplastic lesions. The second system is an organ culture-cell culture system in which small pieces of trachea are grown in organ culture, then epithelial cells are grown from these pieces as primary cell cultures. The organ cultures were exposed to the direct alkylating agent, N-methyl-N'-nitro-N-nitrosoguanidine, MNNG, used as the initiator, then multiple short exposures to TPA are used to promote. Primary cell cultures and cell lines were then established from these explants. After 52 wk, a five-fold increase in the percen tage of explants producing tumorigenic cell lines was observed when MNNG + TPA exposed explants were compared to MNNG exposed explants. Tracheal explants exposed to TPA alone produced many cell lines but none tested were tumorigenic. These two systems provide a means to study tumor promotion in respiratory epithelium. The evidence more importantly suggests that airborne promoting substances may play a key role in the development of bronchogenic carcinoma. (no Refs)

67. PROMOTION OF LUNG TUMORS IN MICE (MEETING ABSTRACT).

Witschi HP

Oak Ridge National Laboratory, Oak Ridge, TN

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Experimental evidence obtained during the last 6 yr shows that several elements of two-stage carcinogenesis apply to the development of lung tumors in Strain A or Swiss-Webster mice. At least three agents which have been identified as promoters in skin, urinary bladder, and liver will also enhance tumor formation in lung: phorbol, saccharin, and butylated hydroxytoluene (BHT). The antioxidant BHT acts in many respects like a typical promoting agent: it is effective if animals are treated after exposure to an initiating agent, but not if they are treated beforehand. Administration of BHT can be delayed up to 5 mo after urethan treatment and still enhance tumor formation. BHT enhances lung tumor formation regardless of its route of administration (ip injection, gavage, or ingestion in the diet). The lowest dose of BHT required to produce an effect has not yet been determined. In at least one mouse strain, BHT also enhances tumor formation in animals initiated with 3-methylcholanthrene or diethylnitrosamine. On the other hand,

no evidence is available yet to show that BHT would enhance tumor development in animals treated with subcarcinogenic doses of an initiating compound. Nor has it been possible to produce more tumors with BHT in mouse strains which have a low spontaneous tumor incidence and respond poorly to urethan. The question has not been resolved whether BHT accelerates growth of preformed tumors only or whether it induces the formation of more tumors. (no Refs)

MUTAGENICITY OF NITROSO COMPOUNDS

68. EFFECT OF CALCIUM PHOSPHATE AND ALUMINA C GAMMA GELS ON THE MUTAGENICITY AND CYTOTOXICITY OF DIMETHYLNITROSAMINE AS STUDIED IN THE CHO/HGPRT SYSTEM.

Tan EL, Hsie AW
Univ. Tennessee-Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 84(1):147-156 1981

The effects of calcium phosphate and alumina C gamma gels in the S9 activation system on the cytoxicity and mutagenicity of dimethylnitrosamine (DMN) were studied in the Chinese hamster ovary cell hypoxanthine-guanine phosphoribosyl transferase system. The calcium phosphate gel in the Ca/Mg-S9 mix was essential in potentiating the mutagenic activity of DMN. Varying amounts of CaCl2 were added to the Mg-S9 salts before adding S9 protein to determine whether the cytotoxic and mutagenic effects of DMN were due to Ca++ in the Ca/Mg-S9 mix. Increasing amounts of CaCl2 in the Mg-S9 mix made up in phosphate buffer caused increased cell killing and mutant induction; the max was observed at a Ca++ concentration of 10 milliM. Increasing concentrations of commercial preparations of calcium phosphate and tricalcium phosphate gels also increased cytotoxicity and mutagenicity of DMN. Alumina C gamma gel in Mg-S9 mix was just as effective as calcium phosphate gel in activating DMN. The cytotoxicity and mutation frequency of DMN were almost identical to those obtained with calcium phosphate gel. Diethylaminoethyl cellulose caused some increase in DMN-induced cytotoxicity but not -mutagenicity. Increasing the contact time between the S9 protein and the S9 salts increased the efficacy with which the S9 mix activated DMN; this was indicative of an adsorptive process by calcium phosphate gel. The results indicated that calcium phosphate or alumina C gamma gels can mimic the effects of cytosolic factors on the microsomes or by concentration of demethylase activity around the cells. (21 Refs)

69. STRUCTURE-MUTAGENICITY ANALYSIS WITH THE CHO/HGPRT SYSTEM.

Hsie AW
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Food Cosmet Toxicol; 19(5):617-621 1981

A mutational system which affects hypoxanthine-guanine phosphoribosyl transferase (HGPRT) activity in Chinese hamster ovary (CHO) cells, the CHO/HGPRT system, was used to study the structure-mutagenicity of 10 carcinogenic alkylating agents and 6 platinum(11) compounds. Cytotoxic and mutagenic effects of the alkylating agents decreased with increasing size of the alkylating group. When the relationship between DNA alkylation and mutation at the hgprt locus of N-nitroso-N-methylurea (MNU) and N-nitroso-N-ethylurea (ENU) was studied, MNU, on an equimolar basis, had 15x the alkylating activity of ENU but only 3x the mutagenic activity. Ethylation of DNA by ENU resulted in greater than 4x the number of mutagenic lesions than did methylation by MNU. cis-Dichlorodiammine platinum(11) was the most mutagenic among the six platinum(1)chloroammines, while its steric isomer, the trans form, was non-mutagenic. Mutagenicity and cytotoxicity differ in their reactivity of DNA binding. The mutation induction by the cis isomer as a function of treatment concentration was 2400x that of the trans isomer. However, the cis isomer bound only 3x more to cellular DNA than did the trans isomer. The mutant yield per molecule bound to DNA was 800x larger for the cis than for the trans isomer. Cytotoxicity per DNA lesion was a factor of 9 greater for the cis than for the trans isomer. These studies demonstrate that both the quantity and quality of DNA adducts affect mutagenicity and cytotoxicity. The CHO/HGPRT system is useful for studying genetic aspects of toxicology and for relating molecular parameters necessary for mutagenic and cytotoxic activities. (26 Refs)

70. QUANTITATIVE MUTAGENESIS AND MUTAGEN SCREENING WITH MAMMALIAN CELLS: TOWARD A COMPREHENSIVE CHINESE HAMSTER GENETIC TOXICITY SYSTEM (MEETING ABSTRACT).

Hsie AW
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Toxicologist; 1(1):40 1981

We have employed Chinese hamster ovary (CHO) cells to develop and define a mutational assay at the hypoxanthine-guanine phosophoribosyl transferase (HGPRT) locus. Coupled with S9 metabolic activation system, the CHO/HGPRT assay permits quantification of gene mutation and cytotoxicity induced by various classes of mutagens including 3 aklanesulfonates, 2 alkylsulfates, 3 nitrosoguanidines, 3 nitrosoureas, 19 heterocyclic mustards (ICR compounds), 6 platinum(II)chloroammines, 7 quinolines, 8 nitrosamines, 3 haloethanes, 4 polyaromatic hydrocarbons. Such study elucidates the structure-activity relationship for a given class of direct-acting mutagens. All carcinogens investigated, except ICR 191, showed mutagenic activity; and all noncarcinogens were nonmutagenic. The CHO/HGPRT system can also simultaneously measure mutagen-induced chromosome aberration and sister chromatid exchange (SCE) which led to the development of the Multiplex CHO Genetic Toxicity Assay. Recent studies have shown that it is feasible to determine chromosomal deletion and loss using a CHO/human hybrid cell line and to develop a Chinese hamster system for studies of induction of mutation at the HGPRT locus, chromosome aberration and SCE of peripheral blood lymphocytes. The use of such a comprehensive Chinese Hamster Genetic Toxicity System consisting of these four assays at the cellular and organismic level should enable a sensitive and reliable identification of suspected environmental mutagens. (no Refs)

71. DIFFERENTIAL INDUCIBILITY OF CHROMOSOME ABERRATIONS AND SISTER-CHROMATID EXCHANGES BY INDIRECT MUTAGENS IN VARIOUS MAMMALIAN CELL LINES.

Ikeuchi T, Sasaki M
(c/o Sasaki) Chromosome Res. Unit, Hokkaido Univ., Sapporo 060, Japan
Mutat Res; 90(2):149-161 1981

A variety of mammalian cell cultures were examined for inducibility of chromosomal aberrations (CA) and sister chroma-

tid exchanges (SCE) by the indirect mutagens cyclophosphamide (CP), dimethylnitrosamine (DMN), and benzo(a)pyrene (BP). Sixteen cell lines were examined for response to CP. All rat ascites hepatoma cell lines showed a significant increase in frequencies of both SCE and CA in a dose-dependent manner. Several rat esophageal tumor cell lines showed an extremely high sensitivity to CP, with sig nificant yields of SCE and CA obtained at much lower concentrations compared to other cell lines. Seven cell lines were examined for their responsiveness to DMN. AH66-B, R1 and R3 cells, which showed a significant response to CP, were also sensitive to DMN in induction of CA. SCE frequency increased only slightly, however. Of the four cell lines studied for BP sensitivity, GHE cells showed the highest response to BP; frequencies of both SCE and CA were increased up to 3.8-and 6.9x. AH66-B and B-13 were moderately sensitive. HE2144 was almost insensitive but showed slightly increased frequency of SCE. (28 Refs)

72. THE RELATIONSHIP BETWEEN THE CARCINOGENICITY AND MUTAGENICITY OF NITROSAMINES IN A HEPATOCYTE-MEDIATED MUTAGENICITY ASSAY.

Jones CA, Marlino PJ, Lijinsky W, Huberman E
(c/o Huberman) Div. Biological and Medical Res., Argonne Natl. Lab., 9700 S. Cass Ave., Argonne, Il, 60439
Carcinogenesis; 2(10):1075-1077 1981

The hepatocyte-mediated mammalian cell mutagenesis assay was used to determine the mutagenic activity of 26 nitrosamines for which a carcinogenic potency could also be established. Mutagenesis was measured in Chinese hamster V79 cells cocultivated with primary rat hepatocytes, which are capable of activating nitrosamines. Resistance to ouabain and to 6-thioguanine served as genetic markers. Carcinogenicity data were obtained from experiments in which groups of male and female Fischer rats were treated with nitrosamines po for 50 wk. A linear relationship between carcinogenicity and mutagenicity was established ($p = 0.0001$). The correlation coefficients at the 6-thioguanine and the ouabain markers were 0.85 and 0.66, respectively. This study demonstrates that the use of intact hepatocytes to activate nitrosamines, coupled with appropriate mammalian target cells to indicate genetic damage, represents a useful system for both detecting and establishing the mutagenicity of a series of nitrosamines in a manner corresponding to the carcinogenic potency produced by the same chemicals in vivo. (24 Refs)

73. A NOVEL MUTANT OF MOUSE LYMPHOMA CELLS SENSITIVE TO ALKYLATING AGENTS AND CAFFEINE.

Shiomi T, Hieda-Shiomi N, Sato K
Div. Genetics, Natl. Inst. Radiological Sciences, 9-1, Anagawa 4, Chiba 260, Japan
Mutat Res; 103(1):61-69 1982

Sensitivity to physical and chemical mutagens was determined for parental mouse lymphoma L5178Y cells, M10 cells (a N-methyl-N'-nitro-N-nitrosoguanidine sensitive strain), and a novel methyl methanesulfonate [MMS] sensitive strain designated MS-1. The mutagens tested were UV, x-rays, 4-nitroquinoline 1-oxide (4NQO), caffeine, and the alkylating agents MMS, ethyl methanesulfonate (EMS), and mitomycin C (MMC). In terms of the D37 values (doses that reduce cell survival to 37%), M10 cells were 2.5-7x more sensitive to EMS, MMC, 4NQO, MMS, and x-rays than were parental L5178Y cells; the new mutant MS-1 was approx 3x more sensitive to MMS, EMS, MMC, and caffeine than were parental cells. Sensitivity characteristics of M10 cells to x-rays, alkylating agents, and 4NQO resemble some ataxia telangiectasia cells. The sensitivities of MS-1 cells to alkylating agents and caffeine are novel among mammalian cell mutants so far reported. The M10 mutant, which is sensitive to MMS and x-rays but not UV, has been stable for approx 1 yr in continuous culture. The MS-1 mutant has been stable in MMS sensitivity for at least 6 mo in continuous culture. (28 Refs)

74. EFFECTS OF 5-METHYLNICOTINAMIDE ON MOUSE L1210 CELLS EXPOSED TO N-METHYL-N-NITROSOUREA: MUTATION INDUCTION, FORMATION AND REMOVAL OF METHYLATION PRODUCTS IN DNA, AND UNSCHEDULED DNA SYNTHESIS.

Durrant LG, Margison GP, Boyle JM
Paterson Laboratories, Christie Hosp. and Holt Radium Inst., Manchester, M20 9BX, England
Carcinogenesis; 2(10):1013-1017 1981

Alkylation of L1210 DNA by N-methyl-N-nitrosourea (MNU) was measured, and the effects of 5'-methylnicotinamide (5MeN) on removal of methylated purines, on unscheduled DNA synthesis, and on induction of 6-thioguanine (6TG)-resistant mutants were examined. The loss of colony-forming ability of L1210 cells caused by MNU was potentiated 2.8-fold in the presence of 1 milliM 5MeN. 5MeN reduced the frequency of 6TG-resistant mutants induced by MNU: In two experiments, the induced mutation frequencies of cells not treated with 5MeN were 15.6 and 12.1 mutants per 10(4) surviving cells per milliM MNU compared with 7 mutants per 10(4) survivors per milliM MNU for mutations expressed and selected in the presence of 5MeN. 7-Methylguanine removal from DNA by MNU was unaffected by 5MeN, whereas O6-methylguanine (O6-MeG) was removed from 5MeN-treated cells at a significantly higher rate (half-life 28 hr) than from untreated cells (half-life 46 hr). 5MeN had no effect on inhibition of normal replicative DNA synthesis by 0.2 milliM hydroxyurea, whereas it stimulated unscheduled DNA synthesis under similar conditions. The observation that 5MeN reduces the frequency of 6TG-resistant mutants induced by MNU and enhances the rate of O6-MeG removal is consistent with this being a promutagenic lesion in L1210 cells. (48 Refs)

75. NEOPLASTIC TRANSFORMATION ASSAY WITH BALB/C 3T3 CELLS. ANALYSIS OF RESULTS WITH 70 CODED SAMPLES (MEETING ABSTRACT).

Sivak A, Lobb AM, Tu AS
Arthur D. Little, Inc., Cambridge, MA, 02140
Toxicologist; 1(1):131 1981

Exposure of certain populations of mouse BALB/c 3T3 cells to chemical carcinogens results in morphological transformation in the cell culture that can be identified and quantified. In the assay validation, 15 uncoded and 70 coded chemicals comprising a series of known carcinogens and noncarcinoge ns were tested using a standard protocol. Among the chemical classes tested, polycyclic aromatic hydrocarbons, direct-acting alkylating agents, activated aromatic amine metabolites and certain metal carcinogens gave positive responses. Aromatic amines, nitrosamines and other chemicals, such as natulan and cyclophosphamide, that require metabolic activation to exhibit activity, did not induce neoplastic transformation, although aniline was positive. The hormones ethynylestradiol, progesterone and diethylstilbesterol, which are likely epigenetic carcinogens, were not active in this system. Statistical analyses of the data reveal that: (1) the range of spontaneous transformation frequency has a mean value of 0.28 foci/plate; (2) the induced

transformation frequency of the positive control (3-methylcholanthrene, 2 ug/ml) has a mean value of 2.6 foci/plate; (3) at control values above the cumulative mean, a doubling of transformation frequency in treated cultures is a statistically significant positive effect (alpha less than or equal to 0.05). At the control values below the cumulative mean, statistical significance is achieved only at higher treated to control response ratios, which rise sharply as control values approach zero. (4) The relationship of the untreated control response to the positive response is not a simple background incidence. (no Refs)

76. EVALUATION OF TRANSFORMATION ASSAYS USING C3H 10T1/2 CELLS FOR USE IN SCREENING (MEETING ABSTRACT).

Schechtman LM, Lubet RA, Kouri RE, Sivak A, Tu AS

Microbiological Associates, Bethesda, MD, 20816

Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

The C3H 10T 1/2 C1 8 (10 T 1/2) cell transformation system is being evaluated independently and simultaneously in two laboratories for its utility, reliability and reproducibility as a predictive in vitro screening test for potential chemical carcinogens. Eleven known chemicals were tested using a standard protocol in the absence of exogenous metabolic activation. The polycyclic hydrocarbon carcinogens 3-methylcholanthrene, 7,12-dimethylbenz(a)anthracene, benzo(a)pyrene (BaP) and dibenz(a,h)anthracene induced Type II and Type III foci, while the non-carcinogens phenanthrene and anthracene were non-transforming. The direct-acting agents N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), ethyl methanesulfonate and N-acetoxy-2-fluorenylacetamide (AFAA) induced little or no transformation. The procarcinogenic aromatic amines N-2-fluorenylacetamide and 2-anthramine were not active. Thus the 'standard' assay shows a range of sensitivity, depending upon the specific class of chemicals employed. To overcome such limitations, the assay has been modified by (a) cell synchronization, (b) increasing cells at risk, (c) replating treated cells ('level II transformation'), and (d) supplying exogenous metabolizing activity (eg hepatocytes, S-9). Transformation of 10T 1/2 cells was induced by MNNG and AFAA using modified protocols without a metabolic supplement. Use of an Aroclor-1254-induced rat hepatic S-9 resulted in activation of a variety of chemicals to cytotoxic metabolites. S-9-mediated enhancement of phenotypic transformation has been thus far achieved with BaP. Additional studies employing hepatocytes for metabolic activation are in progress. Validation studies of cell populations derived from Type III foci showed that while most transformed populations grew in soft agarose, their tumorigenic potential was dependent on the strain, age and immunosuppression of host animals used. Efforts are ongoing to assess the efficacy of these different approaches in rendering the 10T 1/2 cell system responsive to diverse classes of procarcinogens and direct-acting carcinogens. Validation of the transformation system is being carried out by testing coded samples. (no Refs)

77. FAILURE OF CHLOROFORM TO INDUCE CHROMOSOME DAMAGE OR SISTER-CHROMATID EXCHANGES IN CULTURED HUMAN LYMPHOCYTES AND FAILURE TO INDUCE REVERSION IN ESCHERICHIA COLI.

Kirkland DJ, Smith KL, Van Abbe NJ

Toxicol Lab. Ltd., Bromyard Road, Ledbury, Herefordshire HR8 1LG, England

Food Cosmet Toxicol; 19(5):651-656 1981

Mutagenicity of chloroform in Escherichia coli strains WP2p and WP2uvrA-p was tested using both plate incorporation and liquid pre-incubation. In addition, ability of chloroform to induce sister-chromatid exchanges (SCE) in human lymphocytes in the presence of S-9 rat-liver microsomes was tested. Chloroform did not induce reversions in WP2p or WP2urvA-p in either of the assays used. In contrast, both positive control chemicals used (N-methyl-N'-nitro-N-nitrosoguanidine and 2-aminoanthracene) were mutagenic. Benzo-(a)pyrene at concentrations up to 10 ug/ml induced significant increases in SCE in human lymphocytes in the presence or the absence of S-9, whereas chloroform (25-400 ug/ml) plus S-9 induced a significant increase in SCE in cells from the same donor only at the 50-ug/ml dose. Whereas the positive control gave reasonable dose-response trends [correlation coefficient (r) 0.995 and 0.782 with and without S-9, respectively], this was not the case for chloroform ($r = 0.206$). Failure of chloroform to induce any type of mutagenic event in vitro raises questions in relation to prediction of cancer risk. (19 Refs)

78. ETHANOL- OR ACETONE-PRETREATMENT OF MICE STRONGLY ENHANCES THE BACTERIAL MUTAGENICITY OF DIMETHYLNITROSAMINE IN ASSAYS MEDIATED BY LIVER SUBCELLULAR FRACTION, BUT NOT IN HOST-MEDIATED ASSAYS.

Glatt H, De Balle L, Oesch F

(c/o Oesch) Inst. Pharmacology, Univ. Mainz, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany

Carcinogenesis; 2(10):1057-1061 1981

The effect of acetone or ethanol pretreatment of mice on dimethylnitrosamine (DMN) mutagenicity in host- and liver subcellular fraction-mediated assays was investigated. Salmonella typhimurium TA 92 was used in both the in vitro S9-mediated assay and in the in vivo host-mediated assay because it was more sensitive than TA 1535, TA 100, or Escherichia coli WP2 uvrA and because it possesses an intact polysaccharide layer. Pretreatment of C57BL/6J mice with either 45 millimoles of acetone or 30-60 millimoles of ethanol per kg potentiated DMN mutagenicity in S9 mix-mediated assays. At low DMN concentrations (100 uM), greater than 100x more mutants were induced with S9 mix from acetone-treated mice than with S9 mix from controls. Ethanol had a similar, but weaker, effect. In the host-mediated assay, DMN was a potent mutagen, but this effect was not enhanced by pretreatment with either acetone or ethanol. In general, mutagenicity was slightly lower in acetone-pretreated animals than in controls. A possible explanation for the differences observed in vitro and in vivo may be that in vitro the activity of the dilute metabolizing system is limiting for the activation of DMN, whereas in vivo DMN is completely metabolized in both induced and noninduced animals. (16 Refs)

79. TOXICITY, MUTAGENESIS AND CO-MUTAGENESIS OF CADMIUM (CD) IN SALMONELLA MUTANTS TA98 AND TA100 (MEETING ABSTRACT).

Rubin RJ, Kroll R
Department of Environmental Health Sciences, Johns Hopkins University, Baltimore, MD, 21205
Toxicologist; 1(1):25 1981

The role of cadmium as a carcinogen has been controversial. In the widely used bacterial assay of Ames for mutagens/carcinogens the metals have routinely been reported to be negative. In the present study the mutagenesis and co-mutagenesis of Cd along with its toxicity was studied in TA98 and TA100. Cd, at the concentrations indicated, was added to the media used to prepare the solid agar plates onto which the test bacteria were poured. Exposure to Cd occurred during the 48 hr incubations on the solid agar. Toxicity tests were carried out on nutrient agar while mutagenesis and co-mutagenesis were performed on histidine-deficient agar. TA98 was inhibited 50% by 2.5 x 10(-6) M Cd but was uneffected by 2.5 x 10(-8) M and lower; TA100 was less sensitive and was inhibited 50% by 1.25 x 10(-4) M and was uneffected by 2.5 x 10(-5) M and lower. Zn, at non-toxic levels, completely protected against the toxicity of Cd at Zn: Cd M ratios of 4:1 for TA98 and 1:1 for TA100. At nontoxic levels Cd had no mutagenic effect on TA98 but increased the mutagenicity of a known direct-acting mutagen, hycanthone (Hyc) 3-4 fold. The same degree of enhancement of Hyc mutagenicity by non-toxic levels of Cd was seen in TA100. Lucanthone (Luc), an indirect-acting m utagen, has been shown to give rise to Hyc following S9 activation. No effect of Cd was seen on the mutagenicity of Luc in a S9 supplemented system, suggesting inhibition of activation, thereby offsetting Cd enhancement of any Hyc that would be formed. No effect of Cd was seen on another direct-acting mutagen, methylnitro-nitrosoguanidine. These data indicate that Cd may act as a co-mutagen for certain mutagenic agents and suggest a possible co-carcinogenic role for this metal. (no Refs)

80. INVESTIGATIONS ON THE MUTAGENICITY OF PRIMARY AND SECONDARY ALPHA-ACETOXYNITROSAMINES WITH SALMONELLA TYPHIMURIUM: ACTIVATION AND DEACTIVATION OF STRUCTURALLY RELATED COMPOUNDS BY S-9.

Pool BL, Wiessler M
Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
Carcinogenesis; 2(10):991-997 1981

Mutagenicity of 12 primary and secondary alpha-acetoxynitrosamines (AANs) was investigated to elucidate the influence of structure on the extent of their biologic activity. Aldehydes presumably arising after AAN cleavage were nonmutagenic in Salmonella typhimurium strain TA 1535. After hydrolysis, AANs were mutagenic, indicating that AAN mutagenicity is caused mainly by the alkylating species generated after cleavage of the acetates and not by the corresponding aldehydes. More stable primary AANs were less mutagenic at equimolar concentrations than the respective secondary compounds. Addition of S-9 mix caused both activation and deactivation in an unexpected structure-related pattern: An exactly opposite influence of S-9 components on mutagenicity was observed for each pair of primary and secondary AANs containing the same alkylating species. Pairs of compounds with both methylating and ethylating properties were influenced differently by addition of S-9 than those with propylating or butylating properties. This demonstrates how different chemical properties of intermediate forms may influence biologic activity of otherwise similar compounds. (28 Refs)

81. CONVERSION OF CHLORINATED NITROBIPHENYL ETHERS AND THEIR DERIVATIVES TO MUTAGENS BY WHITE-SPOTTED CHAR, SALVELINUS LEUCOMAENIS, LIVER HOMOGENATE.

Miyauchi M, Takagi M
Lab. Food Hygiene, Faculty of Fisheries, Hokkaido Univ., Hakodate 041, Japan
Bull Jpn Soc Sci Fish; 47(2):243-250 1981

Mutations were induced by p-nitrobiphenyl ether, its chlorinated forms, and their nitroso derivatives in a Salmonella typhimurium assay without liver homogenate. Liver homogenate from the white-spotted char increased mutagenicity of the compounds slightly and greatly increased the mutagenicity of amino derivatives. (23 Refs)

82. MUTAGENICITY PATTERNS RESULTING FROM THE REACTION OF NITRITE WITH ICR-170.

de Flora S, Zanacchi P, Camoirano A, Bennicelli C
Inst. Hygiene, Univ. Genoa, Via Pastore 1, 16132 Genoa, Italy
Mutat Res; 103(1):13-17 1982

ICR-170, 2-methoxy-6-chloro-9-(3-[ethyl-2-chloroethyl] aminopropylamino) acridine.2HCl reacted with nitrite in an acidic environment to form a mutagenic derivative. Suitable soln of sodium nitrite were preincubated, either separately or mixed together, with 5 ml of human gastric juice or 0.15 M NaCl adjusted to various pH values. After 60 min at 37 C, 1 ml of 0.2 M phosphate-buffered saline, pH 7.4, was added. The resulting mixtures (0.5 ml/plate) were assayed in the plate incorporation test using various Salmonella his- strains. All the strains except TA1535 were reverted by ICR-170. TA1537 was most sensitive, a finding typical for acridine derivatives. Mutagenicity of TA1537 and of the other positive strains (TA 1538, TA98, and TA100) was increased by rat liver S9 fractions. The metabolic effect was less pronounced than previously reported for the same compound lacking an ethyl group (ICR-191). Direct frameshift activity of ICR-170 decreased in all positive strains after its reaction with nitrite. Such an activity was replaced by an S9-requiring mutagenic response in TA1538, TA98, and TA100; the response correlated with the amounts of both ICR-170 and nitrite. The study suggests that nitrosation of ICR compounds occurs at the only site where ICR-170 and ICR-191 are different, ie, at the terminal nitrogen of the nitrogen-mustard moiety. (10 Refs)

83. A EUROPEAN COLLABORATIVE STUDY OF THE AMES ASSAY: I. RESULTS AND GENERAL INTERPRETATION.

Grafe A, Mattern IE, Green M
Boehringer Mannheim GmbH, Sandhofer Strasse 116, D-6800 Mannheim 31, W. Germany
Mutat Res; 85(6):391-410 1981

The Ames assay was performed for three test compounds (benzo(a)pyrene, N-nitrosomorpholine, and 2-aminoanthracene) in a collaborative study in 19 laboratories. Marked variations between test results occurred between and within laboratories; variability resulted partially from different interpretations of the guidelines, which allowed some flexibility. Results were also affected by other factors. Some variation was due to the level and quality of S9 preparations; different batches of S9 prepared in the same laboratory by a standard procedure may vary significantly in their properties. Other factors involve the number of cells used, differences in culture conditions, type and amount of solvent, number of plates used per concentra-

tion, and method of counting colonies. When results from all experiments were considered together, 60-80% were found within the half- to two-fold range of the overall median. Such a range might be considered satisfactory for a study not using rigidly standardized test conditions. Several recommendations for design and performance of future collaborative studies are given. (13 Refs)

84. INDUCTION OF SKIN PAPILLOMAS IN THE SENCAR MOUSE AS A TIER 2 CARCINOGENESIS BIOA SSAY (MEETING ABSTRACT).

Bull RJ, Robinson M, Glas J, Cmehil D, Orthoefer J
Health Effects Research Laboratory, Cincinnati, OH, 45268
Toxicologist; 1(1):129 1981

The Toxic Substances Control Act mandates the testing of industrial chemicals for which insufficient evidence of safety exists. One of the more critical areas in c'-nical carcinogenesis testing is a dependable approach to confirmatory tests (tier 2) of identifed positives at a screening level (tier 1). The present work was undertaken as part of a systematic evaluation of a series of short-term in vitro and in vivo tests which possess properties thought desirable for tier 2 testing. Experiments were designed to determine whether the mous skin responds to initiating doses of carcinogens selected from he major carcinogen classes administered by four routes, oral, ip, sc and topical. Experiments to date include testing of diethylnitrosamine, urethane, benzene, benzo(a)pyrene, dimethylbenzanthracene (DMBA), aflatoxin B1, methylmethane sulfonate, azobenzene, FANFT and lead acetate. Two wk following application of the initiating doses of each carcinogen a 20 wk promotion schedule involving the application of 1 ug of 12-O-tetradecanoyl phorbol-13-acetate (TPA) was initiated. On the basis of preliminary data it is apparent that papilloma development in response to chemical carcinogens varies with route of exposure. For example, it is apparent that the response to urethane administered po exceeds that observed by the topical route by 3-fold. Conversely, the response of the mouse skin to benzo(a)pyrene is more than 10-fold by the topical vs systemic routes of exposure. Route specific responses to DMBA, benzene, diethylnitrosamine and aflatoxin B1 are also apparent. These results suggest that consideration be given to employing more than one route of exposure in testing of chemicals using the mouse skin initiation/promotion system. (no Refs)

CELLULAR EFFECTS OF NITROSO COMPOUNDS

85. KINETICS OF O6-METHYLGUANINE REPAIR IN HUMAN NORMAL AND ATAXIA TELANGIECTASIA CELL LINES AND CORRELATION OF REPAIR CAPACITY WITH CELLULAR SENSITIVITY TO METHYLATING AGENTS.

Shiloh Y, Becker Y
(c/o Becker) Dept. Molecular Virology, Hadassah-Hebrew Univ. Medical Sch., Post Office Box 1172, 91 010 Jerusalem, Israel
Cancer Res; 41(12):5114-5120 1981

Human lymphoblastoid cell lines from normal individuals and from patients with ataxia telangiectasia were either proficient or deficient in their ability to repair the mutagenic DNA adduct O6-methylguanine that is induced by methylating carcinogens. There was no relationship between the capacity to repair O6-methylguanine and the ataxia telangiectasia phenotype. Time-course studies done following a short pulse (2 min) of alkylation with 0.5 mg of N-[3H]methyl-N'-nitro-N-nitrosoguanidine per ml reveal ed that the repair of O6-methylguanine in human lymphoblastoid lines proficient in this ability is a rapid process, which proceeds with a half-life of 10 to 15 min. Lymphoblastoid lines with deficient capacity to repair this DNA adduct were hypersensitive to the cytotoxic effect of the methylating carcinogens N-methyl-N'-nitro-N-nitrosoguanidine, N-methyl-N-nitrosourea, and methyl methanesulfonate, and this hypersensitivity was correlated with the relative amount of O6-methylguanine induced by each of the three chemicals. This was taken as an indication of the lethality of unrepaired O6-methylguanine. The extent of DNA repair synthesis induced by the three carcinogens was the same in cell lines proficient and deficient in O6-methylguanine repair, indicating no major deficiency in an excision repair pathway in the hypersensitive cell lines. (Author abstract) (44 Refs)

86. CORRELATIONS OF DNA DAMAGE AND REPAIR WITH NUCLEAR AND CHROMOSOMAL DAMAGE IN HELA CELLS CAUSED BY METHYLNITROSAMIDES.

Collins AR, Ord MJ, Johnson RT
Cancer Res. Campaign Mammalian Cell DNA Repair Group, Dept. Zoology, Univ. Cambridge, Downing St., Cambridge, CB2 3EJ, England
Cancer Res; 41(12):5176-5187 1981

N-Methyl-N-nitrosourethan induces breaks or alkali-labile sites in cellular DNA, many if not all of which are repaired rapidly. Other DNA lesions are repaired by an excision process. Hydroxyurea and 1-beta-d-arabinofuranosylcytosine cause an accumulation of DNA breaks after N-methyl-N-nitrosourethan treatment, probably by inhibiting the DNA-synthetic (but not the nucleolytic) stage of excision repair. Chromosome damage (fragmentation or attenuation of interphase chromosomes and decondensation and radial rearrangement of metaphase chromosomes) is present soon after treatment with N-methyl-N-nitrosourethan and is not reversed during further incubation. It is apparently associated with the longer-lived DNA lesions, probably those which are removed by excision, and is enhanced by incubation with hydroxyurea and 1-beta-d-arabinofuranosylcytosine. N-Methyl-N-nitrosourethan also inhibits cellular protein and DNA synthesis and causes the dispersion of polysomes and the loss of nucleolar structure. N-Methyl-N-nitrosourea is less potent than N-methyl-N-nitrosourethan in causing DNA or chromosome damage and is less cytotoxic. (Author abstract) (72 Refs)

87. THE MECHANISM OF ACTION OF 1-(2-CHLOROETHYL)-3-(METHYL-ALPHA-D-GLUCOPYRANOS-6-YL) 1-NITROSOUREA (MCNU) IN CULTURED HELA S3 CELLS (MEETING ABSTRACT).

Kanamaru R, Kakuta H, Sato T, Sato K, Sugawara K, Wakui A
The Research Institute for Tuberculosis and Cancer, Tohoku University, Sendai, Japan
Twenth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Colony formation was inhibited completely by treatment of cultured HeLa S3 cells with MCNU at 200ug/ml for 60 min. Drug concentration required for 50% inhibition was 40 ug/ml. When the cells were incubated with [14C-Ethylene]MCNU, the radioactivity bound to acid-insoluble fraction was increased linearly, however, in case of [14C-Glucose]MCNU, little or no radioactivity was detected, suggesting that MCNU possesses a strong alkylating activity and a weak carbamoyling activity.

Compared with RNA and protein synthesis, DNA synthesis was considerably more suppressed. At 100 ug/ml, DNA, RNA and protein synthesis was inhibited by 75, 17 and 4%, respectively. Single strand scission of DNA was observed 24 hr after treatment at 100 ug/ml for 60 min. Although remarkable unscheduled DNA synthesis was induced at this time, no rejoining of the damaged DNA occurred even after 48 hr, suggesting that the last step of repair process of DNA, ligation of the nicked strand, was inhibited. (1 Ref)

88. DAMAGING EFFECTS OF FOURTEEN CHEMOTHERAPEUTIC DRUGS ON MOUSE TESTIS CELLS.

Meistrich ML, Finch M, Da Cunha MF, Hacker U, Au WW
Dept. Experimental Radiotherapy, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Cancer Res; 42(1):122-131 1982

The harmful effects of 14 chemotherapeutic drugs on spermatogenesis in the mouse have been evaluated by studies of testicular cell killing and morphological and genetic damage produced. Male mice were given drugs as single injections at various doses up to the toxic levels. Prednisone and 6-mercaptopurine produced little or no cytotoxicity. All other drugs tested killed differentiated spermatogonia. Of these, methotrexate, cyclohexylchlorethylnitrosourea, cis-platinum, and mechlorethamine did not show significant stem cell killing. Bischlorethylnitrosourea, chlorambucil, 5-fluorouracil, mitomycin C, actinomycin D, and procarbazine showed some stem cell killing. Triethylenethiophosphoramide (thio-TEPA) was the only drug in this group which killed large numbers of stem cells. Only 5-fluorouracil and cis-platinum killed spermatocytes, and only cis-platinum killed spermatids. Several drugs induced chromosome breaks in treated spermatocytes. thio-TEPA was effective in inducing chromosome translocations in treated spermatocytes and probably also in spermatocytes which originated from surviving treated stem cells. It had been our hypothesis that the cytotoxic effects of these drugs on mouse testicular stem cells would correlate with the duration of azoospermia observed in patients. This was shown not to be the case. Thus, the cytotoxic effects of single injections of single chemotherapeutic agents on the mouse testis did not appear to be predictive of which drugs will cause long-term azoospermia in humans. (Author abstract) (50 Refs)

89. EFFECT OF 1,2-DIMETHYLHYDRAZINE AND DIETHYLNITROSAMINE ON CELL REPLICATION AND U NSCHEDULED DNA SYNTHESIS IN TARGET AND NONTARGET CELL POPULATIONS IN RAT LIVER FOLLOWING CHRONIC ADMINISTRATION.

Lewis JG, Swenberg JA
(c/o Swenberg), Chemical Industry Inst. Technology, Research Triangle Park, NC, 27790
Cancer Res; 42(1):89-92 1982

Marked differences in the rates of de novo DNA synthesis and unscheduled DNA synthesis were observed in hepatocytes and nonparenchymal cells (NPC) isolated from Fischer 344 rats following in vivo exposure to 1,2-dimethylhydrazine (SDMH) or diethylnitrosamine (DEN) for 1.5, 4, 8, 16, and 28 days. Liver cells were labeled in vivo with bromodeoxyuridine and [3H]thymidine, following which, hepatocytes and NPC were separated by elutriation centrifugation. Purified DNA was then separated into fully replicated and nonreplicated DNA by ultracentrifugation in CsCl gradients. Following exposure to SDMH, the rate of de novo DNA replication in NPC was greatly increased over both control NPC and the corresponding hepatocytes for the entire time course. Unscheduled DNA synthesis was only observed in hepatocytes after exposure to SDMH. Following exposure to DEN, both cell populations exhibited changes in de novo DNA synthesis that were directly proportional to one another except at 1.5 days. Increases occurred first in hepatocytes at 1.5 days but were delayed in NPC until 4 days. Hepatocyte replication returned to control values by 28 days. Unscheduled DNA synthesis was much lower following exposure to DEN than SDMH. Therefore, SDMH, which induces hemangioendotheliomas of the liver at the dose given, induces a marked increase in cell replication in the target cell population and unscheduled DNA synthesis in the resistant cell population. DEN, which induces hepatocellular carcinoma, moderately stimulates cell replication in both liver cell populations and induces little unscheduled DNA synthesis in either population. (Author abstract) (19 Refs)

90. NON-RANDOM DISTRIBUTION OF N-METHYL-N-NITROSOUREA SENSITIVE SITES IN A EUKARYOTIC GENOME.

Werner D, Hadjiolov D, Hershey HV
Inst. Cell and Tumor Biology, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Chem Biol Interact; 37(3):279-287 1981

DNA released from Ehrlich ascites cells by lysis in the presence of 50 ug x ml-1 of proteinase K contains long alkali-stable strands in the order of 50-100 x 10(6) daltons. In contrast, DNA released in the presence of 6 mg x ml-1 of autodigested pronase is significantly nicked. According to sedimentation rates the number of internal ends liberated during this procedure is 24/200 x 10(6) daltons. The number of alkali-labile sites introduced into DNA by incubation of Ehrlich ascites cells with 1 mM of N-methyl-N-nitrosourea (MNU) followed by cell lysis in the presence of 50 ug x ml-1 of proteinase K and alkali-denatur ation is 16.6/200 x 10(6) daltons. From this one should expect that denatured DNA released from cells pretreated with 1 mM of MNU which are subsequently lysed with 6 mg x ml-1 of pronase would have about 40 single-strand breaks/200 x 10(6) daltons. However, denatured DNA strands released by 6 mg x ml-1 of pronase either from MNU-treated or untreated cells cannot be separated by centrifugation through alkaline sucrose gradients. This phenomenon could be explained by a non-random distribution of MNU-inducible alkali-labile sites of DNA in vivo. (Author abstract) (11 Refs)

91. NEOPLASTIC TRANSFORMATION OF HUMAN EPITHELIAL CELLS IN VITRO AFTER EXPOSURE TO CHEMICAL CARCINOGENS.

Milo GE, Noyes I, Donahoe J, Weisbrode S
Comprehensive Cancer Center, Ohio State Univ., 410 West 12th Ave., Columbus, OH, 43210
Cancer Res; 41(12):5096-5102 1981

Human foreskin epithelial cells were transformed to an anchorage-independent state of growth (in soft agar) and neoplasia (invasion of chick embryonic skin in vitro). Aflatoxin B1, N-methyl-N'-nitro-N-nitrosoguanidine, propanesultone, beta-propiolactone, or UV absorbance at 254 nm were used successfully as carcinogens. These foreskin epithelial cells, like human foreskin fibroblasts, were readily transformed when treated in S phase but, unlike the transformed fibroblasts, expression of cellular neoplasia did not require an extended period of time in culture. The invasive features of the transformed human epith-

elial cells in chick embryonic skin in vitro simulated squamous cell carcinoma. (Author abstract) (29 Refs)

92. MEMBRANE GLYCOPEPTIDES FROM CHEMICALLY TRANSFORMED CELLS: COMPARISON BETWEEN MESENCHYMAL AND EPITHELIAL CELL LINES DERIVED FROM DIMETHYLNITROSAMINE-TREATED RAT KIDNEY.

Rachesky MH, Hard GC, Glick MC
(c/o Hard), Fels Res. Inst., Temple Univ. Sch. Medicine, 3420 North Broad St., Philadelphia, PA, 19140
Cancer Res; 42(1):39-43 1982

The membrane glycopeptides of normal and chemically transformed malignant cell lines derived from rat kidney were investigated by gel permeation chromatography. The cell lines, which were metabolically labeled with L-[5,6-3H]fucose or D-[6-3H]glucosamine, were derived from rats treated in vivo with a carcinogenic dose of dimethylnitrosamine to induce both mesenchymal and cortical epithelial tumors in the rat kidney. Among the cell lines examined were: (a) transformed lines of mesenchymal type derived from the rat kidney 2 to 24hr after the dose of carcinogen; (b) mesenchymal tumor cell lines obtained from the dimethylnitrosamine-induced mesenchymal tumors occurring at 7 to 10 mo; (c) a transformed epithelial cell line derived from rat kidney 48 hr after the carcinogenic dose; and (d) an epithelial cell line obtained from a renal adenocarcinoma induced at 10 mo by a dose of diethylnitrosamine. For control comparisons, populations o f normal renal epithelium and mesenchyme were cultured selectively from untreated rats. The radioactive glycopeptides of the neoplastic epithelial cell lines (transformed and tumor) displayed a shift to more complex higher-mol-wt glycopeptides when compared with the normal epithelial counterparts. These results were similar to those reported previously for other cell types. In contrast, the neoplastic cell lines of mesenchymal origin lacked higher-mol-wt glycopeptides, displaying patterns that were identical with those of normal renal mesenchymal cells. It is suggested from these results that the membrane glycopeptide alterations characteristic of virus-transformed and other tumor cells are not detected by these techniques in all cell lines transformed by chemical agents. Furthermore, cell lineage within the same organ may play a role in the observed difference. (Author abstract) (22 Refs)

93. EFFECT OF ANTINEOPLASTIC AGENTS ON THE INDUCTION OF SUPPRESSOR MACROPHAGES BY CONCANAVALIN A-BOUND TUMOR VACCINE.

Kataoka T, Oh-Hashi F, Sakurai Y, Ogihara K
Div. Experimental Chemotherapy, Cancer Chemotherapy Center, Japanese Foundation for Cancer Res., Kami-Ikebukuro 1-37-1, Toshima-ku, Tokyo 170, Japan
Cancer Res; 41(12):5151-5157 1981

The present study was undertaken to identify tumor vaccine-induced suppressor cells and to examine the effect of antineoplastic agents on their production and suppressor activity. Primary and secondary sensitization with concanavalin A (con A)-bound L1210 murine leukemia cell vaccine induced suppressor cells in the peritoneal cavity of histocompatible BALB/c x DBA/2Cr F1 mice. These cells phagocytized latex beads and adhered to plastic vessels. Their suppressor cell activity, determined by polyclonal in vitro spleen cell blastogenesis, was abrogated by silica but not by rabbit anti-mouse brain antiserum and complement. This evidence led to the conclusion that the suppressor cells were macrophages. The production of suppressor macrophages depended on both the Con A-free vaccine cells and vaccine-bound Con A molecules since, singly, neither induced the corresponding suppressor cell activity. Although the induced suppressor cells were not abrogated by mitomycin C in vitro and cyclophosphamide in vivo, the increase of peritoneal suppressor cells following the second vaccination and/or their suppressor activity was significantly inhibited by antineoplastic agents including cyclophosphamide, mitomycin C, and 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2 chloroethyl)-1-nitrosourea hydrochloride. The finding that vinblastine preferentially inhibited the increase of peritoneal suppressor cells suggested that these agents interfered with the proliferation of suppressor cells (and/or their progenitor cells) in response to the second vaccination. The close correlation between the potency of these antineopl astic agents in inhibiting the production of suppressor cells and the induction enhanced antitumor immunity by Con A-bound tumor vaccine supports the feasibility of the proposed combination of chemotherapy and immunotherapy in which antineoplastic agents are dually effective by killing tumor cells and eliminating the vaccine-associated suppressor cells. (Author abstract) (11 Refs)

94. RESPONSIVENESS OF FETAL RAT BRAIN CELLS TO GLIA MATURATION FACTOR DURING NEOPLASTIC TRANSFORMATION IN CELL CULTURE.

Haugen A, Laerum OD, Bock E
Lab. Experimental Pathology, Div. Cancer Cause and Prevention, NIH, Bethesda, MD, 20205
Acta Pathol Microbiol Scand [A]; 89(5):393-402 1981

The effect of partially purified extracts from adult pig brains containing a glia maturation protein factor (BE) has been investigated on neural cells during carcinogenesis. Pregnant BD IX-rats were given a single transplacental dose of the carcinogen ethylnitrosourea (EtNU) on the 18th day of gestation. The brains of the treated fetuses were transferred to cell culture and underwent neoplastic transformation with a characteristic sequence of phenotypic alterations which could be divided into five different stages. During the first 40 days after explanation (Stage I and II) BE induced morphological differentiation of epithelioid neural cells into astrocytes; this occurred in carcinogen treated cells as well as in untreated control cultures. At the same time cells with astrocyte morphology showed accumulation of glial fibrillary acidic protein (GFA) as tested by indirect immunofluorescence with monospecific antibodies against GFA. Thereafter, in the EtNU pre-treated cultures an increased number of cells with astrocyte morphology was seen, and BE further increased the number of cells with long cytoplasmic processes. Control cells were GFA negative, while some few strongly, as well as many weakly, positive cells were seen after treatment with BE (Stage III). At the later stages of neoplastic transformation the effect of BE became gradually less, and in tumorigenic cells which occurred after about 200-300 days, only a slight morphological change took place in a few cell lines. No appreciable effect on GFA-content was seen any longer, although some few weakly GFA positive cells could be observed in all permanent cell lines. Fetal rat brain cells therefore seem to become less responsive to this differentiation inducer during neoplastic transformation in cell culture. (Author abstract) (36 Refs)

95. DEOXYRIBONUCLEIC ACID METHYLATION IN HUMAN CELLS EXPOSED TO NITROSOCIMETIDINE.

Jensen DE
Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Biochem Pharmacol; 30(20):2864-2867 1981

DNA methylation rates and methylated purine yields are reported for Raji cells exposed to nitrosocimetidine (NC), methylnitrosourea, and N-methyl-N'-nitro-N-nitrosoguanidine. NC was unique relative to the other two compounds in that it hydrolyzed only very slowly in cellular growth medium and methylated DNA in rapidly growing cells slowly but persistently. (26 Refs)

TRANSPLACENTAL EFFECTS OF NITROSO COMPOUNDS

96. THE FATTY ACID PATTERN OF CENTRAL MYELIN LIPIDS AFTER TRANSPLACENTAL INTOXICATION BY ETHYLNITROSOUREA.

Wender M, Zorawski A, Adamczewska-Goncerzewicz Z, Mularek O
Dept. Neurology, Acad. Medicine, 49 Przybyszewskiego Str., 60-355 Poznan, Poland
Exp Pathol; 19(4):226-238 1981

Porton mice were used in the experiments. Pregnant animals were injected iv with a single dose of ethylnitrosourea (ENU). The poison was administered at the 15th day of pregnancy. The cerebral myelin of offsprings of the intoxicated mothers was examined with respect to the fatty acid spectrum of myelin lipids. The results obtained lead to the following conclusions: The fatty acid pattern of the individual myelin lipid fractions has revealed significant differences between the normal myelin and that isolated from brains of mice that had been subjected to transplacental intoxication by ENU. Transplacental intoxication by ENU has not only a carcinogenic effect on the CNS, but it obviously also affects the lipid metabolism of membranous structures of the developing brain. ENU when acting during fetal life induces the formation of deviated myelin, that differs significantly with respect to its lipid and fatty acid composition from that of normally developing animals. (Author abstract) (14 Refs)

97. STUDY ON THE TRANSPLACENTAL AND POSTNATAL MODEL OF CARCINOGENESIS IN MICE (MEETING ABSTRACT).

Rossi L, Cabral JR, Della Prota JR
Division of Experimental Oncology A, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy
Toxicologist; 1(1):154 1981

A study is reported on the cumulative carcinogenic effect of transplacental and postnatal administration of dimethylnitrosamine (DMN), urethane, ascorbic acid, cyclophosphamide, isoniazid, 3-(5-nitro-2-furyl)-imidazo (1,2-alpha)pyridine (NFIP) and rifampicin. DMN and urethane were administered in the drinking water to CTM outbred mice for periods covering pregnancy and/or lactation. The other compounds were given po or ip (cyclophosphamide) during pregnancy and lactation. A control group was available. The progeny of all treated animals was killed at 60 wk of age and the progeny of a further rifampicin-treated groups was killed at 90 wk of age. Under the present experimental conditions the group treated with isoniazid, rifampicin, ascorbic acid and cyclophosphamide showed no differences in tumor incidence when compared with controls. DMN, urethane and the nitrofuran NFIP induced multiple tumors at various sites. The present experiments indicate that DMN is not a transplacental carcinogen because a significant increase of tumors was observed only in the progeny exposed during the lactation period. Urethane was shown to be a transplacental carcinogen. Mice exposed to the nitrofuran NFIP during prenatal and postnatal period showed a clear carcinogenic response. The latter result is a further indication of the strong carcinogen effects of nitrofurans. The evidence here presented indicates that this biological model may prove useful for screening the potential carcinogenicity of chemicals. (no Refs)

IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS

98. ALPHA-FETOPROTEIN: CELLULAR ORIGIN OF A BIOLOGICAL MARKER IN RAT LIVER UNDER VARIOUS EXPERIMENTAL CONDITIONS.

Kuhlmann WD
Lab. Experimental Medicine and Immunocytochemistry, Institut fur Nuklearmedizin, D.K.F.Z., D-6900 Heidelberg, W. Germany
Virchows Arch [Pathol Anat]; 393(1):9-26 1981

Alpha1-fetoprotein (AFP) was detected by serological, light and electron microscopic methods in various experimental models. These included (a) liver regeneration after partial hepatectomy or CCl4 intoxication (mouse and rat); (b) liver intoxication by high doses of N-nitrosomorpholine (NNM) and chemical induction of hepatomas (rat). AFP levels varied greatly according to the animal species and strains used. Low and high AFP-producing species and strains were distinguished. In liver regeneration after hepatectomy or CCl4 intoxication, cellular AFP was found in the cytoplasm of hepatocytes. In NNM-intoxicated livers, elevated AFP levels were associated with proliferation of canalicular epithelial cells in which AFP was localized. In early stages of hepatocarcinogenesis, significant AFP increase occurred after high-dose carcinogen feeding and AFP was also localized in proliferating canalicular epithelial cells. On low-dose NNM feeding, no cellular AFP was detected unless hepatomas had developed. At the stage of malignant conversion, distinct AFP staining and non-AFP staining hepatocellular carcinomas appeared in livers. (Author abstract) (69 Refs)

99. GUINEA-PIG AFP DURING NORMAL ONTOGENESIS, LIVER CARCINOGENESIS, AND UNDER HORMONE TREATMENTS (MEETING ABSTRACT).

Gourdeau H, Belanger L
Molecular Oncology Laboratory, Laval University, Quebec City, Quebec, Canada
Oncodev Biol Med; AbstractsBook,1:P6 1981

Guinea-pig alpha fetoprotein (AFP) was purified to homogeneity, characterized, and a radioimmunoassay was developed. Serum AFP level in fetal guinea-pig remains in the mg/ml range up to the 8th gestational wk and then drops rapidly. The electrophoretic and lectin affinity molecular variants of AFP change during ontogenesis, probably in relation with changes in carbohydrate composition of the protein. The liver and the yolk sac are the main sites of AFP synthesis during fetal life with the stomach and the small intestine contributing

smaller amounts, as measured by peptide pulse labeling assays in vivo. Compared to other species, serum AFP levels are very high in normal adult guinea-pig; these levels are reduced dramatically by administration of glucocorticoids or ACTH. The hormone effect is rapidly reversed upon withdrawal. In guinea-pigs fed with diethylnitrosamine, serum AFP increases at the time liver tumors appear; there is no early induction and the increase is much less than in rats under similar treatment. (no Refs)

100. EXPRESSION OF ALPHA-FETOPROTEIN AND ALBUMIN GENES IN A RAT HEPATOMA CELL LINE SY/1/80: EVIDENCE FROM THE NEED OF SPECIES SPECIFIC SERUM FACTORS.

Selten GC, Selten-Versteegen AM, Yap SH
Dept. Medicine, St. Radboud Hosp., Univ. Nijmegen, 6500 HB Nijmegen, The Netherlands
Biochem Biophys Res Commun; 103(1):278-284 1981

The requirement for rat serum factors to express the alpha-fetoprotein (AFP) and albumin genes in rat hepatoma cell line SY/1/80 is reported. SY/1/80 is a cell line derived from a diethylnitrosamine-induced rat hepatoma. The original tumor produces both AFP and globin protein. During in vitro passage of cells in medium supplemented with calf, horse or human serum, the mRNAs for these proteins could not be detected. Supplementation of cultures with rat serum induced the appearance of both AFP and globin mRNAs. While the nature and mechanisms of such species-specific serum factors remains to be elucidated, this observation may explain the inability of cells passaged in calf serum to produced specific proteins in a continuous fashion. (19 Refs)

EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS

101. INCREASE IN FAECAL NITROSAMINES IN JAPANESE INDIVIDUALS GIVEN A WESTERN DIET.

Suzuki K, Mitsuoka T
Animal Physiology Lab., Inst. Physical and Chemical Res., Wako-shi, Saitama 351, Japan
Nature; 294(5840):453-456 1981

Levels of five volatile nitrosamines were studied in six healthy Japanese men (27-39 yr old) given Japanese and Western diets. Three subjects received, in order: (1) a typical Japanese diet for 4 days; (2) a mixed Japanese diet (ie, items from Western, Chinese, and typical Japanese diets) for 3 days; (3) a balanced Western-style diet for 8 days followed by a typical Japanese diet for 6 days. Four subjects received a long-term mixed Japanese diet followed by a high-fat diet containing a large proportion of meat for 4 days. The av level of total volatile nitrosamines in the feces of subjects receiving the Western-style diet was 10x that in feces of subjects receiving the Japanese diet. The max level of total nitrosamines was 26.6 ug/kg. Feces of subjects receiving the Japanese diet contained N-nitroso-dimethylamine (NDMA), N-nitrosodibutylamine (NDBA), and N-nitrosopyrrolidine (NPYR) at levels less than 1.7 ug/kg. After 3 d ays on the mixed Japanese diet, N-nitrosopiperidine (NPIP) appeared in the feces, and the NPYR concentration increased. When the subjects were given the Western diet, the levels of these nitrosamines increased markedly, particularly NPIP, which reached a max of 13.3 ug/kg. The max level of fecal N-nitrosodiethylamine was 1.8 ug/kg during the experiment, and there was no clear relationship between the level of this nitrosamine and change in diet. Nitrosamine levels decreased when subjects were receiving the high-fat, high-meat diet. these results suggest that fecal nitrosamines are formed in the intestine from precursors contained in meat and vegetables. (27 Refs)

102. ASSOCIATION OF DIET AND PLACE OF BIRTH WITH STOMACH CANCER INCIDENCE IN HAWAII JAPANESE AND CAUCASIANS.

Kolonel LN, Nomura AM, Hirohata T, Hankin JH, Hinds MW
Epidemiology Program, Cancer Center Hawaii, Univ. Hawaii, 1236 Lauhala St., Suite 407, Honolulu, HI, 96813
Am J Clin Nutr; 34(11):2478-2485 1981

Stomach cancer incidence rates were compared among four groups: Japanese in Japan, Japanese in Hawaii, Caucasians in Hawaii, and all American whites. The highest rates at all ages occurred in the Japan Japanese, followed next by the Hawaii Japanese. Hawaii Caucasians tended to have similar age-specific rates to American whites in general. When the Japanese and Caucasians in Hawaii were divided by place of birth, the Japanese migrants to Hawaii had higher age-adjusted incidence rates than the Japanese born in Hawaii, while the Caucasian migrants to Hawaii (chiefly from the United States mainland) had lower rates than the Caucasians born in Hawaii. Examination of dietary data in relation to the place-of-birth-specific incidence rates showed positive associations of stomach cancer with consumption of rice, pickled vegetables, and dried/salted fish, and a negative association with vitamin C intake. The results are consistent with the particular hypothesis that stomach cancer is caused by endogenous nitrosamine formation from dietary precursors, and that vitamin C may protect against the disease. (Author abstract) (43 Refs)

103. NITRITE STABILITY AND NITROSATION POTENTIAL IN HUMAN GASTRIC JUICE.

Tannenbaum SR, Moran D, Falchuk KR, Correa P, Cuello C
Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Cancer Lett; 14(2):131-136 1981

Human gastric juice from patients free of chronic atrophic gastritis (CAG) and intestinal metaplasia (IM) was shown to contain factors which rapidly destroy nitrite. Continued generation of nitrite as a result of hypochlorhydria was found to deplete gastric juice of its protective factors and lead to an elevated rate of nitrosation. It is suggested that ascorbic acid and alpha-tocopherol may be useful in areas where gastric cancer is prevalent since these drugs destroy nitrite. (17 Refs)

104. ETIOLOGY AND PREVENTION OF GASTRIC CANCER (MEETING ABSTRACT).

Stemmermann GN
No affiliation given
First UICC Conference on Cancer Prevention in Developing Countries, August 25-29, 1981, Nagoya, Japan. International Union Against Cancer 368 pp., 1981.

Three conditions have been identified as precursors to gastric cancer: Atrophic gastritis of the oxyntic mucosa, atrophic gastritis with intestinal metaplasia of the antral mucosa, and partial gastrectomy with gastroenterostomy. Mutagenic nitroso compounds have been identified in the gastric mucosa or gastric juice in each of these precursor states, and it is likely that

these compounds are formed in the stomach itself. Identification of persons with these diseases is now possible, and this should identify asymptomatic persons who are most likely to benefit from a selective diagnostic screening program. The benefits of selective diagnostic screening for gastric cancer would probably be too few and too costly to justify its use in any but high risk areas, even when the cost of the procedure is minimized by the use of paramedical personnel. The use of vitamin C and E supplements to suppress endogenous nitrosation in high risk persons could be justified on theoretical grounds, but there is no hard evidence that this would lower the risk of gastric cancer. On a mass scale, however, it would be comparatively inexpensive and would do no harm. The potential benefits of vitamin supplements to large numbers of high risk persons need not be delayed since assessment of the efficacy of this form of intervention can be performed synchronously by following small, defined sub-groups of high risk persons. (no Refs)

105. ANTITUMOR EFFECTS OF HYDROGEN PEROXIDE IN VIVO.

Nathan CF, Cohn ZA
Rockefeller Univ., New York, NY, 10021
J Exp Med; 154(5):1539-1553 1981

Antitumor activity of hydrogen peroxide (HP) against P338 lymphomas and P815 mastocytomas in female (BALB/c x DBA/2)F1 (CD2F1) mice was studied. Glucose oxidase was injected in free form (GO) or bound to latex beads (GOL). GOL suspension contained an av 5.8 x 10(10) beads/ml and produced an av 172 nanomoles H2O2/min. Binding of GO to beads prevented dispersal of GO from the injection sites. In mice injected with 10(6) P338 cells, 1 ml GOL increased survival time an av 3.2 days. Soluble GO produced no increase in survival. GOL was effective if injected up to 1 hr before P338 injection, but not if injected earlier. Exposure of mice to 100% O2 for 2-3.5 hr following GOL and P338 injection increased survival time an av 4.7 days. Supplemental glucose had no effect on survival time. Injection of beads bound with catalase abolished the antitumor effect of GOL, indicating that the effect of GOL was dependent on H2O2. Although no cures were obtained with injection of 10(6) P338 cells, cures were obtained with lower tumor cell doses. The LD50 of G OL against P815 tumors was 4.2x as great as for P338. P815 susceptibility to GOL was increased 5.5x by injection of 30 mg 1,3-bis(2-chloroethyl)-1-nitrosourea/kg body wt with GOL treatment. No toxic effects were noted for GOL, although preformed H2O2 was toxic. (42 Refs)

REVIEWS INCLUDING NITROSO COMPOUNDS

106. NUTRITION AND CANCER: A REVIEW.

Muller E, Rickenbach M
Institut fur Sozial- und Praventivmedizin, Universitat Zurich, Gloriastrasse 32 B, 8006 Zurich, Switzerland
Praxis; 70(43):1903-1912 1981

The possible roles of various nutrients in carcinogenesis are reviewed. Epidemiological studies indicate a high rate of carcinomas of the breast (BC) and colon (CC) in industrialized countries. Dietary factors are suggested by changes in cancer frequencies among immigrant populations and their descendants. Dietary studies indicate a positive correlation between dietary fat and CC and BC, as well as a negative correlation between these cancers and dietary fiber content. Animal studies have shown a cancer-promoting effect for fats, particularly unsaturated fats. Fats may promote cancer by affecting specific intestinal bacterial populations, bile secretion, hormonal balance, and immune response. Fiber may reduce cancer risk by speeding the movement of carcinogens through the digestive tract. Cancer risk has not been confirmed for proteins or their pyrolysis products. Some studies have indicated risk associated with pickled, smoked, or fried foods related to production of nitrosamines and nitrosamides. These compounds, which have been shown to be carcinogenic, are formed in vitro from nitrites and secondary amines. Their formation appears to be limited by the presence of ascorbic acid or vitamin E. Further studies of dietary factors are indicated. (130 Refs) (In GER)

107. CHEMICAL AND ENVIRONMENTAL AGENTS IN GASTROINTESTINAL CARCINOGENESIS.

Deschner EE, De Cosse JJ, Sherlock P
Lab. Digestive Tract Carcinogenesis, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Clin Gastroenterol; 10(3):755-771 1981

A review is presented of incidence, risk factors, and chemical and environmental agents involved in induction or promotion of cancer of the gastrointestinal system. Presence of ingested agents in foods and experimental and clinical evidence for cancer causation are discussed. Carcinogenesis is considered with respect to the esophagus (nitrosamines, mycotoxins, promotional factors), stomach (nitrites and polycyclic hydrocarbons, mycotoxins, agricultural products, polychlorinated biphenyls, experimental carcinogens), and large bowel (nitrites, aflatoxins, diet, carrageenan, chemical carcinogens: nitroso compounds, biphenyls, symmetrical 1,2-dialkylhydrazines and azoalkanes and azoxyalkanes). Chemicals with known gastric tumor induction capability in animals are tabulated from published reports. (74 Refs)

108. ROLE OF NUTRITIONAL FACTORS IN REALIZATION OF BIOLOGICAL EFFECTS OF XENOBIOTICS.

Sharmanov TS
Kazakh Branch, Inst. Nutrition, Alma-Ata, USSR
Vopr Pitan; (5):51-57 1981

The role of nutritional factors in the metabolism of pesticides, nitrosamines, and aflatoxins is reviewed. Nitrites present in canned meat or fish can react with exogenous amines to yield carcinogenic nitroso compounds. Dietary deficiency of vitamin C and essential amino acids enhanced the carcinogenic activity of N-nitrosopiperidine in guinea pigs. Deficiency of the essential amino acids and retinol enhanced the incidence of aflatoxin B1-induced tumors in rats. (33 Refs) (In RUS)

109. OCCURRENCE OF LARGE INTESTINE CANCER AND THE ROLE OF INTRALUMINAL BACTERIA.

Hirono I
Cancerous Substances Res. Dept., Tokyo Univ. Sch. Medicine Res. Inst., Tokyo, Japan
Nippon Rinsho; 39(5):32-35 1981

Intestinal bacteria convert some of the free bile acid released into the small intestine eventually from chenodeoxycholic acid, deoxycholic acid, lithocholic acid, etc into secondary bile salts that have effects as promoters of large intestinal tumor growth. When large amounts of fats are consumed, more bile salts are

released into the small intestine, and a greater amount of bile salts are potentially not reabsorbed for reuse in the liver; thus, the unabsorbed bile salts that travel into the large intestine are converted into potential carcinogenic promoters by the bacteria. The bacterial flora in the intestine and frequency of cancer of the large intestine varies according to geographic location, suggesting a causal link. Bacteria in the transverse colon can produce N-nitrosamine compounds from amines and nitric acid that is not excreted in the urine. However, if the fiber content of the feces is sufficient, the feces moves rapidly through the large bowel and direct contact of the carcinogens with the luminal wall is minimal. Roles of various types of bacteria in production of other large intestinal carcinogens have been shown, but explanations of the carcinogenic mechanisms are still being investigated. (14 Refs) (In JPN)

110. ADVANCES IN CARCINOMA OF THE OESOPHAGUS.

Silber W
Dept. Surgery, Medical Sch., Observatory, Cape, South Africa
S Afr Cancer Bull; 25(1/2):24-30 1981

Epidemiology, etiology, diagnosis, and treatment of esophageal carcinoma (EC) are discussed. Incidence of EC can vary 500-fold from one geographic area to another. The highest incidence of EC occurs in economically less advanced countries where population data are inadequate and cancer registration is difficult. In view of the increased incidence of EC in the Cape Colored male, the life style of this group is being studied with emphasis on drinking and smoking habits and other hazards to which members may b e exposed. EC seems to be multifactorial in origin. Risk factors, such as tobacco and alcohol, are considered. Factors related to increased incidence of EC in Transkei, including level of minerals in rocks, soil, or plants, low levels of plant nutrients, manganese deficiency-induced itamin C deficiency in plants, fungus infected maize, and nitrosamine levels are considered. A gross deficiency of serum beta-carotene has been found in an asymptomatic Black male group from a high-risk area in Transkei. Besides prevention, early diagnosis is the only method for improving the otherwise poor diagnosis for EC. Screening and diagnostic techniques for EC are described. Therapeutic techniques for EC are discussed. (14 Refs)

111. ADVANCES IN EXPERIMENTAL CANCER OF THE OESOPHAGUS.

van Rensburg SJ
Natl. Res. Inst. for Nutritional Diseases, P.O Box 70, Tygerberg 7505, South Africa
S Afr Cancer Bull; 25(1/2):66-76 1981

A review and assessment is presented of a biological program conducted during the past 15 yr. Initially acute toxicities of nitrosamines and the pathogenesis of esophageal carcinogenesis were studied. Attempts to identify carcinogens by biological means in high risk populations were largely futile. Acute and chronic studies of nitrosamines, especially N-nitrosomethylpentylnitrosamine, in rats and primates are reported. Short-term induction of neoplasia was studied in rats. Various studies are reported which attempted to identify carcinogenic environmental agents by biologic screening methods. Rats were maintained on food from homes of esophageal cancer sufferers in rural Transkei. Snuff, tobacco and beer from the same area were also examined. Such studies yielded no esophageal carcinoma but only possibly preneoplastic changes. Studies are underway to detect possibly promoting and inhibitory actions of many minerals, vitamins and simulated staple diets on esophageal carcinogenesis, with use of a short-term induction model. A significant promoting action of even subclincal zinc deficiency has been described. There is also evidence of promoting actions of magnesium, nicotinic acid and riboflavin deficiency, as well as by high intakes of vitamin A, when other beneficial nutrients are marginally available. (15 Refs)

112. THE PROBLEM OF CANCERIGENIC ESOPHAGEAL LESIONS.

Mastroviti GD, Zelli GP
Istituto III Clinica Chirurgica, Universita degli Studi di Roma, Roma, Italy
Ann Ital Chir; 53(1):71-93 1981

Different aspects of cancerigenic esophageal lesions were discussed. Conditioning factors like genetic, geographic, alimentary, socioeconomic, hygienic, infectious, iatrogenic (bougienage), alimentary traumatic (alcohols, nitrosamines and aflatoxins) and etiological factors of known and unknown origin could interact. The importance of controlling systematically and periodically all esophageal dis eases was stressed. The current trend is prophylactic therapy: dietetic, medical, and surgical. (60 Refs) (In ITA)

113. MALIGNANT BRAIN TUMORS.

Bennett JM
Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY
Practical Cancer Chemotherapy. Rosenthal SN, and Bennett JM, ed. Garden City, NY, Medical Examination Publishing Co., 461 pp., 1981.

Pathology, clinical manifestations, diagnosis, and treatment are reviewed. Malignant brain tumors are the second most common cause of cancer deaths among children less than 15 yr old but occur less commonly among adults. The cause is unknown. Classification is complicated by the use of several different systems, but glioblastoma multiforme and Stage I-III astrocytomas are the most common forms in adults. Approx 2-4% of brain cancers are sarcomas. Symptoms are produced by invasion or compression of adjacent structures, increase in intracranial pressure, and herniation of uninvolved brain tissue; symptoms include headache, vomiting, change in mental function or state of consciousness, and dementia. Diagnosis is by recognition of symptoms and by computed tomography. Neurosurgical exploration and maximal tumor removal are advised in all cases. Radiation therapy (5,000-7,000 rads over 6-8 wk) is the primary postoperative treatment. Hypoxic sensitizers such as metronidazole and misonidazole improve the effectiveness of irradiation. Chemotherapy has not been well-studied. Nitrosoureas appear to produce the greatest response rate (up to 50% for a period of several wk). Combined modality therapy produces the best results, but no therapy has produced more than a small increase in survival time. (16 Refs)

114. LEUKEMOGENIC EFFECT OF URETHANE ADMINISTERED TOGETHER WITH ESTROGENS TO MICE.

Bojan F, Gomba Sz, Kertai P
Kozegeszsegtani es Jarvanytani Intezet, Debreceni Orvostudomanyi Egyetem, Debrecen, Hungary
Egeszsegtudomany; 25(3):251-255 1981

Effects of carcinogenic and noncarcinogenic substances administered together with estrogens or urethane were studied in 6-8-wk-old male CFLP mice. Each substance was administered

in three individual doses during an 18-day period, and the results were evaluated after 300 days. Lung tumors and lymphomas were found in the animals treated with ethyl formate (500 mg/kg), phenylurethane (100 mg/kg), pyrene (5 mg/kg), and their combinations with diethylstilbestrol (DES: 25 mg/kg), but there was no significant difference in the percentage of tumor-bearing animals between the treated animals and the untreated controls. Other groups were treated with dimethylnitrosamine (10 mg/kg), benzo(a)pyrene (5 mg/kg), or 3-methylcholanthrene (5 mg/kg), or their combinations with DES. There was no significant difference in tumor frequency between the groups treated with the carcinogens only and those treated with the carcinogens and DES . Solid tumors in the abdominal cavity and hepatic tumor were also found in addition to lung tumors and lymphomas in the DES-treated groups. Other groups were treated with urethane with or without BCG or Escherichia coli endotoxin (ET): the carcinogenic effect of urethane was not modified by BCG and ET. In other experiments, urethane induced multiple lung tumors with and without DES, but the number of lymphomas was significantly higher in the group treated with urethane and DES than in the groups treated with urethane or DES alone. (24 Refs) (In HUN)

* U.S. GOVERNMENT PRINTING OFFICE : 1982—361-847/114

AUTHOR INDEX WITH CITATION NUMBERS

Adamczewska-Gon..... 96
Angsubhakorn S..... 21
Appel KE..... 8
Arfellini G..... 1
Arita N..... 40
Au WW..... 88
Babaya K..... 55
Balanski RM..... 45
Balls M..... 41
Bannasch P..... 16
Bannasch P..... 35
Bar V..... 53
Barbason H..... 14
Becker Y..... 85
Belanger L..... 99
Benfield JR..... 34
Benner U..... 16
Bennett JM..... 113
Bennicelli C..... 82
Beraud M..... 7
Betz EH..... 14
Bhamarapravati..... 21
Birt DF..... 50
Blagoeva PM..... 45
Bock E..... 94
Bodell WJ..... 32
Bojan F..... 114
Borzsonyi M..... 53
Boyle JM..... 74
Britt AL..... 47
Brittebo EB..... 20
Buettner L..... 18
Bull RJ..... 84
Bunte H..... 51
Cabral JR..... 97
Camoirano A..... 82
Chen CB..... 4
Chmiel JS..... 55
Clapp NK..... 6
Clawson GA..... 9
Clothier R..... 41
Cmehil D..... 84
Cohen SM..... 63
Cohn ZA..... 105
Collins AR..... 86
Correa P..... 103
Creasia DA..... 33
Csik M..... 53
Cuello C..... 103
Curphey TJ..... 25
Da Cunha MF..... 88
Dalbey W..... 54
Daugherty JP..... 6
De Balle L..... 78
De Cosse JJ..... 107
De Flora S..... 82
De Ridder L..... 13
Della Prota JR..... 97
Dent JG..... 46
Derache R..... 7
Deschner EE..... 107
Digernes V..... 59
Donahoe J..... 91
Donnelly T..... 30
Durrant LG..... 74
Falchuk KR..... 103
Finch M..... 88
Fischer AH..... 49
Frank N..... 8
Fukushima S..... 44
Gaillard D..... 7
Githens S..... 27
Glas J..... 84
Glatt H..... 78
Glick MC..... 92
Goldfarb S..... 58
Gomba Sz..... 114
Gourdeau H..... 99
Grafe A..... 83
Graichen ME..... 46
Green M..... 83
Grilli S..... 1
Hacker HJ..... 16
Hacker U..... 88
Hadjiolov D..... 90
Hagiwara A..... 44
Hague BF..... 33
Hankin JH..... 102
Hard GC..... 92
Hasegawa R..... 44
Hasegawa R..... 57
Haugen A..... 94
Hayakawa T..... 40
Hecht SS..... 3
Hecht SS..... 4
Hecht SS..... 65
Hecker LI..... 5
Heger RA..... 51
Herren SL..... 47
Herren SL..... 56
Hershey HV..... 90
Hicks RM..... 62
Hieda-Shiomi N..... 73
Hinds MW..... 102
Hirohata T..... 102
Hirono I..... 109
Hirose M..... 44
Hoffmann D..... 65
Hohenstein J..... 51
Hollenberg P..... 23
Hsie AW..... 68
Hsie AW..... 69
Hsie AW..... 70
Huberman E..... 72
Hurter T..... 39
Ichinose M..... 37
Iino S..... 37
Ikeuchi T..... 71
Imaida K..... 57
Ito N..... 44
Ito N..... 57
Ito N..... 64
James JL..... 9
Jensen DE..... 95
Johnson RT..... 86
Jones CA..... 72
Jordan VC..... 49
Kakuta H..... 87
Kanamaru R..... 87
Kataoka T..... 93
Kato A..... 40
Kertai P..... 114
Khoury M..... 47
Kirkland DJ..... 77
Klimek F..... 16
Knowles K..... 41
Kobori O..... 37
Koen H..... 58
Kokkinakis D..... 23
Kolonel LN..... 102
Kouri RE..... 76
Krech R..... 35
Kreja L..... 43
Kroll R..... 79
Kuhlmann WD..... 98
Laerum OD..... 94
Langhans P..... 51
Lawrence JF..... 12
Lawson T..... 24
Leduc R..... 12
Leonard TB..... 46
Lewis JG..... 89
Lijinsky W..... 17
Lijinsky W..... 18
Lijinsky W..... 19
Lijinsky W..... 2
Lijinsky W..... 72
Liu SF..... 11
Lobb AM..... 75
Longnecker DS..... 25
Lubet RA..... 76
Margison GP..... 74
Marlino PJ..... 72
Marxer A..... 52
Mastroviti GD..... 112
Mattern IE..... 83
Mayer A..... 42
Mayer D..... 16
McClusky GA..... 18
McClusky GA..... 5
Meistrich ML..... 88
Mennel HD..... 39
Miki K..... 37
Milo GE..... 91
Mirvish S..... 22
Mitsuoka T..... 101
Miyata Y..... 55
Miyauchi M..... 81
Miyazaki J..... 37
Mogami H..... 40
Moody DE..... 9
Moore M..... 16
Moran D..... 103
Mosselmans R..... 13
Mularek O..... 96
Muller E..... 106
Nagel D..... 22
Nathan CF..... 105

Nettesheim P. 54
Nishitoi H. 38
Niwa H. 37
Nomura AM. 102
Noonan JJ. 48
Noyes I. 91
Oda T. 37
Oesch F. 78
Ogihara K. 93
Oh-Hashi F. 93
Oka H. 37
Ord MJ. 86
Orthoefer J. 84
Oyasu R. 55
Pak HY. 34
Pereira MA. 47
Pereira MA. 56
Pereira MA. 61
Pinter A. 53
Pipy B. 7
Pool BL. 80
Popp JA. 46
Pour P. 31
Pour PM. 30
Pour PM. 50
Prodi G. 1
Pugh TD. 58
Rachesky MH. 92
Raleigh JA. 11
Rao MS. 23
Rao MS. 29
Reber HA. 31
Reuber MD. 17
Reuber MD. 19
Reznik-Schuller. 33
Rickenbach M. 106
Riggs CW. 17
Robinson M. 84
Rocchi P. 1
Romagna F. 15
Romruen K. 21
Rose DP. 48
Rose DP. 49
Rossi L. 97
Rubin RJ. 79
Ruby JR. 27
Ryan JJ. 12
Sahaphong S. 21
Sakurai Y. 93
Sasaki M. 71
Sato K. 73
Sato K. 87
Sato T. 87
Scarpelli DG. 23
Scarpelli DG. 29
Schechtman LM. 76
Schlake W. 51
Schmidt-Ruppin. 52
Seidel HJ. 43
Selten GC. 100
Selten-Versteeg. 100
Sharmanov TS. 108
Sherlock P. 107
Shiloh Y. 85
Shiomi T. 73
Silber W. 110
Singer B. 32
Singer GM. 18
Singer GM. 19
Sivak A. 75
Sivak A. 76
Smith J. 22
Smith KL. 77
Smuckler EA. 9
Spengler S. 32
Sridhar R. 10
Steele VE. 66
Stemmermann GN. 104
Subbarao V. 29
Sugawara K. 87
Surjan A. 53
Suzuki H. 37
Suzuki K. 101
Swenberg JA. 89
Takagi M. 81
Tan EL. 68
Tannenbaum SR. 103
Teplitz RL. 34
Tjalve H. 20
Torok G. 53
Tsuda H. 57
Tu AS. 75
Tu AS. 76
Tweedie JH. 31
Underwood B. 2
Ushio Y. 40
Van Abbe NJ. 77
Van Rensburg SJ. 111
Vesselinovitch. 58
Wakui A. 87
Wallcave L. 22
Wanson JC. 13
Weisbrode S. 91
Wender M. 96
Werner D. 90
Whelan JF. 27
Wiessler M. 8
Wiessler M. 80
Witschi HP. 67
Woolley PV. 26
Woolley PV. 28
Wynder EL. 65
Yager JD. 60
Yamada K. 40
Yang P. 28
Yantchev IK. 36
Yap SH. 100
Yerino P. 26
Yokota S. 34
Young R. 3
Young R. 4
Zanacchi P. 82
Zbinden G. 15
Zelli GP. 112
Zerban H. 16
Zerban H. 35
Zorawski A. 96
Zurlo J. 25

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

DIETARY FACTORS IN CARCINOGENESIS

1. NUTRITION AND ENVIRONMENTAL HEALTH: THE INFLUENCE OF NUTRITIONAL STATUS ON POLLUTANT TOXICITY AND CARCINOGENICITY. VOLUME 2: MINERALS AND MACRONUTRIENTS.

Calabrese EJ

Environmental Health Program, Div. Public Health, Univ. Massachusetts, Amherst, MA

Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Toxicity and Carcinogenicity. Volume 2: Minerals and Macronutrients. New York, John Wiley and Sons, 468 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

2. RETROSPECT AND PROSPECT OF STUDIES ON DIGESTIVE SYSTEM DISEASES IN CHINA.

Zhang X

Dept. Internal Medicine, Capital Hosp., Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Zhonghua Xiaohua Zazhi; 1(1):1-4 1981

In CHI

3. EPIDEMIOLOGY OF PITUITARY ADENOMAS.

Gold EB

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:163-183 1981

4. BLADDER CANCER EPIDEMIOLOGY.

Mataneski GM, Elliott EA

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 North Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:203-229 1981

5. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.

Ernster VL

Dept. Epidemiology and International Health, 1699HSW, Univ. California, San Francisco, CA, 94143

Epidemiol Rev; 3:184-202 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

6. AIR POLLUTION AND BIOLOGICAL DEFENCE.

Schlipkoter HW, Dolgner R

Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany

Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

In GER

7. CANCER AND THE PHYSICOCHEMICAL QUALITY OF DRINKING WATER IN QUEBEC.

Thouez JP, Beauchamp Y, Simard A

Dept. Geography, Univ. Montreal, Montreal, Quebec, Canada

Soc Sci Med [Med Geogr]; 15(1):213-223 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

8. ONCOGENIC VIRUSES.

Wyke JA

Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

J Pathol; 135(1):39-85 1981

9. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.

Essex M, Grant CK, Cotter SM, Hardy Jr WD

Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115

Haematol Blood Transfus; 26:483-487 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

10. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASAYS: A REPORT OF THE U.S. EPA'S GENE-TOX PROGRAM.

Preston RJ, Au W, Bender MA, Brewen JG, Carrano AV, Heddle JA, McFee AF, Wolff S, Wassom JS

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Mutat Res; 87(2):143-188 1981

11. BACTERIAL SYSTEMS FOR CARCINOGENICITY TESTING.

Mohn GR

Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands

Mutat Res; 87(2):191-210 1981

12. MUTAGENESIS BY CHEMICAL AGENTS IN V79 CHINESE HAMSTER CELLS: A REVIEW AND ANALYSIS OF THE LITERATURE.

Bradley MO, Bhuyan B, Francis MC, Langenbach R, Peterson A, Huberman E

Merck Inst. for Therapeutic Res., West Point, PA, 19486

Mutat Res; 87(2):81-142 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER BIOLOGY.

Ruddon RW

Biological Markers Program, NCI-Frederick Cancer Res. Center, Frederick, MD

Cancer Biology. New York, Oxford University Press, 344 pp., 1981.

14. AVOIDABLE CANCER: ATTRIBUTION OF RISK.

Doll R

Radcliffe Infirmary, Oxford, England

S Afr Cancer Bull; 25(3):125-146 1981

Keep Up with the Cancer Literature

Each Month
You Can Receive Abstracts
Covering Your Specialty Area

- This convenient service — called Auto SDI* — is as near as your nearest biomedical library. Discuss your research interests with the librarian who will design an appropriate search strategy.
- Abstracts of the latest published literature are searched automatically each month and those related to your interests are delivered to you on a regular basis.
- The abstracts you receive are selected from more than 4,000 monthly entries made into CANCERLIT — the extensive cancer literature data base of the National Cancer Institute.

Talk With Your Librarian
About the Auto SDI Service TODAY.

*Auto SDI stands for Automatic Selective Dissemination of Information. It is a service provided to you, at minimal cost, by the International Cancer Research Data Bank (ICRDB) — a part of the National Cancer Institute.

VIDEOTAPES

ON CURRENT TOPICS IN CANCER RESEARCH

A pilot project of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute

Three series are available . . .

THE RELATION OF CARCINOGEN ACTION ON DNA TO CELL TRANSFORMATION

PETER MAGEE Fels Research Institute	*Keynote Address*	#VK01 28 min.
JAMES K. SELKIRK Oak Ridge National Laboratories	*Metabolic Activation and Macromolecular Binding of Chemical Carcinogens*	#VK02 51 min.
PHILIP C. HANAWALT Stanford University	*Cellular Responses to Damaged DNA*	#VK03 54 min.
CHARLES HEIDELBERGER University of Southern California	*Mutagenesis and Oncogenic Transformation of Mouse Embryo Cells*	#VK04 54 min.
FRED RAPP Milton S. Hershey Medical Center	*The Interaction of Herpesviruses and Host Cells Leading to Latency or Transformation*	#VK05 52 min.
	Panel Discussion	#VK06 31 min.

MECHANISMS OF METASTASIS

ISAIAH FIDLER Frederick Cancer Research Center	*The Heterogeneous Nature of Cancer Metastasis and Implications for Therapy*	#VB01 47 min.
GEORGE POSTE Smith, Kline and French Laboratories	*Phenotypic Analysis of Metastatic Cell Populations*	#VB02 42 min.
LANCE LIOTTA National Cancer Institute	*Tumor Cell Invasion of Basement Membranes and Extracellular Matrices*	#VB03 33 min.
EVERETT SUGARBAKER Miami Cancer Institute	*Some Clinical Characteristics of Metastasis in Man*	#VB04 41 min.

AUTOMATED CYTOLOGY

Part One: Principles and Techniques	#VB05 56 min.
Part Two: Biological Applications	#VB06 52 min.

VIDEOTAPES ON CURRENT TOPICS IN CANCER RESEARCH are in the 3/4" U-matic format and can be played on video equipment which accepts the NTSC standard (the standard for videotapes produced in the U.S.).

The videotapes are available on a loan basis. If you would like to schedule viewing for your group, or for more information, please write to:

Cancer Information Dissemination and Analysis Center (CIDAC)
Franklin Research Center
20th and Benjamin Franklin Parkway
Philadelphia, PA 19103

Please specify three choices for viewing dates, and the tapes desired.

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
5285 Port Royal Road
Springfield, Va. 22161

OFFICIAL BUSINESS

Penalty for Private Use, $300

PRINTED MATTER

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF COMMERCE
COM-211

THIRD CLASS
BULK RATE

U.S.MAIL

CK-01

CANCERGRAMS are distributed for the International Cancer Research Data Bank (ICRDB) by the National Technical Information Service (NTIS). CANCERGRAMS are available from NTIS on a standing order basis at $2 each for North American Continent addressees and $3 each for other addressees. An NTIS deposit account is required. For a list of subject categories or other information, please write to:

Subscription Section
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161

NOTICE OF MAILING CHANGE

☐ Check here if you wish to discontinue receiving this publication.

☐ Check here if your address has changed and you wish to continue receiving this publication. (Be sure to furnish your complete address including zip code.)

Tear off cover with address label still affixed and send to:

Computer Support Center
ICRDB Program
IIT Research Institute
10 West 35th Street
Chicago IL. 60616

CK 01/82/05

NCI/ICRDB/CK01 82/05

PB82-935105

ICRDB CANCERGRAM

CHEMICAL CARCINOGENESIS

Nitroso Compounds

SERIES CK01 No. 82/05 MAY, 1982

This Cancergram is a service of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM of the U.S. National Cancer Institute. Every few weeks, an updated Cancergram containing abstracts of selected cancer-related articles recently published in more than 3000 journals, and dealing with the topic indicated by the above title, is sent to researchers working in this area. These researchers are identified on the basis of the description of their current research project that has been submitted to the ICRDB Program, directly or via granting agencies.

This Cancergram is prepared by the Cancer Information Dissemination and Analysis Center (CIDAC) for Carcinogenesis Information. ***If this Cancergram is useful and valuable, please send your comments to the CIDAC address below, since future editions depend on user satisfaction and user needs:***

CIDAC FOR CARCINOGENESIS INFORMATION
SCIENCE INFORMATION SERVICES
FRANKLIN INSTITUTE RESEARCH LABORATORIES
20TH AND RACE STREETS
PHILADELPHIA, PA 19103

NEWARK PUBLIC LIBRARY

MAY 17 19[illegible]

U. S. GOVT. PUBS.
DEPOSITORY 376

VIDEOTAPES ON CURRENT TOPICS IN CANCER RESEARCH ARE NOW AVAILABLE ON LOAN FROM THE ICRDB PROGRAM. SEE THE BACK PAGES OF YOUR CANCERGRAM FOR DETAILS.

In this issue:

- FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS..... 1-2
- INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS..... 3-11
- MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS..... 12-17
- MUTAGENICITY OF NITROSO COMPOUNDS..... 18-23
- CELLULAR EFFECTS OF NITROSO COMPOUNDS..... 24-32
- IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS..... 33
- EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS..... 34-40

FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS

1. FORMATION OF N-NITROSO COMPOUNDS IN FOODS.

Gray JI
Dept. Food Science and Human Nutrition, Michigan State Univ., East Lansing, MI, 48824
ACS Symp Ser; 174:165-180 1981

N-nitrosamines have been found in many food systems including cured meat products, nonfat dried milk, dried malt,

and beer. Possible formation of N-nitrosoamines in these food products is reviewed. Mechanism of N-nitrosopyrrolidine (NPYR) formation, factors influencing NPYR formation, and formation of non-volatile N-nitroso compounds are discussed. (90 Refs)

2. BLOCKING NITROSATION REACTIONS IN VIVO.

Mergens WJ, Newmark HL
Hoffmann-La Roche Incorporated, 340 Kingsland St., Nutley, NJ, 07110
ACS Symp Ser; 174:193-205 1981

Blocking mechanism and the influence of normal dietary components on nitrosation reactions in vivo are presented. Formation of N-nitroso compounds, sources of amines, sources of nitrosating agents, and chemistry of blocking reactions in aqueous and nonaqueous systems are discussed. Ascorbic acid and dl-alpha-tocopherol have been found to be extremely efficient inhibitors of nitrosation reactions in vivo. (62 Refs)

INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS

3. COMPARATIVE CARCINOGENESIS BY SOME ALIPHATIC NITROSAMINES IN FISCHER RATS.

Lijinsky W, Reuber MD
Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Lett; 14(3):297-302 1981

The ability of nitrosodimethylamine (NDMA), nitrosodiethylamine (NDEA), nitrosomethylethylamine (NMEA), nitrosodi-n-propylamine (NDPA), and nitrosodi-isobutylamine (NDBA) to produce tumors in Fischer 344 rats was studied. Twenty 7-8 wk old rats were administered carcinogen at 20 ml/day/rat, 5 days/wk for 30 wk, and were then observed until natural death occurred. Rats received total doses as follows: NDMA, 99 mg; NDEA, 99 mg; NMEA, 450 mg NDPA, 135 mg; NDBA, 2,200 mg. Of 20 NDMA-treated animals, 18 developed tumors compared to 20/20 NDEA-treated, 19/20 NMEA-treated, 20/20 NDPA-treated, and 20/20 NDBA-treated rats. NDBA was the least potent carcinogen in terms of survival time; it produced tumors mainly of the upper respiratory tract, particularly the nasal cavity, and papillomas in the trachea. Structure-activity relationships of the compounds are discussed. (8 Refs)

4. DOSE RESPONSES OF FIVE HEPATOCARCINOGENS FOR THE INITIATION OF RAT HEPATOCARCINOGENESIS.

Imaida K, Shirai T, Tatematsu M, Takano T, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Cancer Lett; 14(3):279-283 1981

Dose response curves were generated for hepatocarcinogenesis in male Fischer 344 rats initiated by diethylnitrosamine (DEN), aflatoxin-B1 (AFB), N-2-fluorenylacetamide (FAA), 3'-methyl-4-dimethylaminobenzene (DAB), or dimethylnitrosamine (DMN). Two wk after initiation, animals were placed on a 0.02% FAA diet for 2 wk. Animals were partially hepatectomized (PH) at the end of wk 3 and killed at the end of wk 4. All five hepatocarcinogens exhibited clear dose response curves for initiation of hepatocarcinogenesis; both numbers and areas of hyperplastic nodules increased with increasing doses in all cases. AFB was the most potent initiator, and was effective at a dose as low as 0.25 mg/kg body wt. Sizes of nodules induced by DEN, FAA, and DMN were smaller than those induced by AFB and DAB. (12 Refs)

5. EFFECTS OF STRUCTURE ON THE CARCINOGENIC BEHAVIOR OF NITROSAMINES.

Wishnok JS
Dept. Nutrition and Food Sciences, Massachusetts Inst. Technology, Cambridge, MA, 02139
ACS Symp Ser; 174:77-87 1981

Small, closely-related series of nitrosamines have been examined and a quantitative structure-activity model (QSM) based on molecular descriptors (physicochemical, geometrical, topological, and electronic) has been developed. The final form of QSM can be interpreted in terms of the proposed mechanisms of action or of modified aspects of these mechanisms. Nitrosamines are highly sensitive towards one or a few target organs. Test compounds included 13 dialkylnitrosamines which induced tumors in the liver or in the lung or esophagus. All test compounds were administered at equal daily doses. Relative properties of compounds reflect then only the differences in the molecular structure of the test substances. The model for organ selectivity requires terms for the parent nitrosamine as well as for the hypothesized metabolites while the model for potency variations contains terms only for the unmetabolized parent compound. (29 Refs)

6. STRUCTURE-ACTIVITY RELATIONSHIPS AMONG N-NITROSO COMPOUNDS.

Lijinsky W
Chemical Carcinogenesis Program, Fredrick Cancer Res. Center, Fredrick, MD, 21701
ACS Symp Ser; 174:89-99 1981

Carcinogenic nitrosamines not mutagenic to Salmonella when activated with rat liver S9 and target organs, were studied. Structures of 4-substituted nitrosopiperidines, beta-substituted nitrosomethylethylamines, and oxygen-containing cyclic nitrosoamines are shown. Carcinogenesis in rats by nitrosomethylalkylamines included relative carcinogenic potency and rat target organ is reviewed. (23 Refs)

7. PATHOGENESIS OF LUNG TUMORS INDUCED BY N-NITROSOHEPTAMETHYLENEIMINE IN F344 RATS.

Reznik-Schuller HM, Gregg M
Frederick Cancer Res. Center, P.O. Box B, Frederick, MD, 21701
Virchows Arch [Pathol Anat]; 393(3):333-343 1981

Male F344 rats were given 3 mg N-nitrosoheptamethyleneimine (NHMI) per 100 g in olive oil by gavage twice a wk for a max of 20 wk. They were killed at predetermined intervals after the start of treatment and the sequential development of NHMI-induced squamous carcinomas in the lungs was followed by light and electron microscopy. Hypertrophy of the endoplasmic reticulum in mucous and Clara cells seen in an initial study suggested that these cells were involved in metabolic activation of the nitrosamine. Basal cells were identified as the cell type that later responded by proliferation, hyperplasia, and squamous metaplasia. Only in the bronchioles, where basal cells are not found in the healthy rat, did these lesions progress further to form squamous cell carcinomas. (Author abstract) (13 Refs)

8. T-CELL LEUKEMIA INDUCED BY 1-PROPYL-1-NITROSOUREA IN FISCHER RATS.

Imamura N, Saito O, Doby H, Ogiu T
Dept. Internal Medicine, Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi 1-2-3, Hiroshima, Japan
Experientia; 37(12):1339-1340 1981

T-cell leukemia was induced at a high rate in female Fischer rats by continuous oral administration of 1-propyl-1-nitrosourea. No association of oncorna viruses were found in the leukemogenesis. (Author abstract) (10 Refs)

9. GASTRIC ULCERS AND PRODUCTION OF GASTRIC CARCINOMA IN DOGS AND RATS: GASTRIC CARCINOMA INDUCED BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE (MNNG) OR N-ETHYL-N'-NITRO-N-NITROSOGUANIDINE (ENNG) (MEETING ABSTRACT).

Koyama Y, Ohmori K, Maruyama K, Hirota T, Ushio K
Dept. Surgery, Natl. Cancer Center Hosp., Chuo-ku, Tokyo 104, Japan
Program and Abstracts of the 37th Meeting of Japanese Research Society for Gastric Cancer in Tokyo, 3 July, 1981. Japanese Research Society for Gastric Cancer, Tokyo 113, Japan, 6, 1981.

In the first experiment, nine beagles in which ulcers were produced in the stomach by electric cautery were given drinking water containing 50 ug of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) per ml for 10 mo, and autopsies were performed 12-64 mo later. Six gastric carcinomas were produced in the nine beagles. Three of the carcinomas (2 signet ring cell carcinomas and 1 differentiated carcinoma) were formed at the artificial ulcerative scar. There were two carcinomas without ulcers (signet ring cell carcinoma and differentiated carcinoma) and one carcinoma with an ulcer which was not artificial. In the second experiment, after two beagles were given a 0.1% indoacetamide (IAM) soln for 3 mo, they were given food soaked in a 150 ug of N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) per ml soln and IAM for 10 mo. A diffuse erosive change occurred in the beagles which were given IAM singly, but the change was enhanced by the addition of ENNG, and carcinoma developed after 12-13 mo and the beagles died within 2 yr. Little erosive change occurred in the beagles which were given ENNG singly and microcarcinoma appeared 9-20 mo later. In the third experiment, an ulcer produced by cautery or by IAM was also the most common site of the MNNG-induced gastric carcinoma in Wistar rats. Therefore, an ulcerative lesion is considered to be the site of action of the carcinogenic factor. (no Refs) (In JPN)

10. CARCINOGENS ON REGENERATION. EFFECT OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE AND 4-NITROQUINOLINE-1-OXIDE ON LIMB REGENERATION IN ADULT NEWTS.

Tsonis PA, Eguchi G
Inst. Molecular Biology, Nagoya Univ., Nagoya 464, Japan
Differentiation; 20(1):52-60 1981

A microcrystal (ca 5 ug) of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) or 4-nitroquinoline-1-oxide (4NQO) was directly administered to the regeneration blastema on Day 7 after amputation of a forelimb in the newt in order to analyze the effect of such potent carcinogenic substances on regenerati on cells. Although neither MNNG nor 4NQO arrested regeneration completely, they caused great retardation of the regeneration cone formation followed by various abnormalities in the bony structures. Abnormal regenerants could be classified into the following four categories; (1) complete absence of both ulna and radius; (2) subregeneration or superregeneration of carpals and digits; (3) multiple disorganization of skeletal elements; (4) arrest of regeneration at the stage of regeneration cone. The polarity of regenerants developed after application of MNNG or 4NQO was very often shifted, during which the regeneration cone was always formed from the site where a microcrystal of the carcinogens was administered. The secondary regeneration initiated by reamputation of the regenerating limb, which had received the carcinogens at the early blastema stage, proceeded in the same way as observed in the case of a simple amputation. This suggested local and temporal effects of the carcinogens applied. Nevertheless, tumor formation has not induced in the newt limb so far. We can learn from these data that both MNNG and 4NQO only alter behavior of the newt regeneration cells without exerting their carcinogenic effects on them, and that the newt cells are highly resistant and stable against the above-mentioned carcinogens. (Author abstract) (14 Refs)

11. STUDIES OF EXPERIMENTAL OLIGODENDROGLIOMA WITH SPECIAL REFERENCE TO THE ULTRASTRUCTURE AND IMMUNOHISTOCHEMICAL LOCALIZATION OF S-100 PROTEIN, GLIAL FIBRILLARY ACIDIC (GFA) PROTEIN AND GALACTOCEREBROSIDE.

Takahashi K
First Dept. Pathology, Sch. Medicine, Gunma Univ., Maebashi-shi, Gunma Pref. 371, Japan
No To Shinkei; 33(7):703-714 1981

Ethylnitrosourea-induced experimental oligodendrogliomas in rats were investigated by light and electron microscopy and immunohistochemically with antisera to S-100 and GFA proteins and anti-galactocerebroside antibody. Sixty-six neuronal and non-neuronal tumors were produced in 44 litters treated with ethylnitrosourea through the mothers; 43 were in the CNS. Twenty-six of the tumors were oligodendrogliomas, of which 7 showed the histology typical of oligodendroglioma and 19 that of oligodendroglioma mixed with astrocytoma or anaplastic glioma. S-100 and GFA proteins were located immunohistochemically. Astrocytic elements showed positive staining for S-100 and GFA proteins. Anaplastic glia were also weakly positive. No GFA protein was found in oligodendroglioma tumor cells. Some of the oligodendroglioma cell nuclei contained S-100 protein. The cytological distribution of galactocerebroside was determined with immunoperoxidase. Galactocerebroside was detected in interfascicular cells in the white matter as well as in normal ependymal cells and choroid plexus epithelium, but the component cells of oligodendroglioma were negative. Electron microscopy of eight tumors showed loosely arranged small dark cells with very scanty cytoplasm and a few, delicate, short cytoplasmic processes. Occasional cells contained a microtubular structure about 25 nm in width dispersed in the cytoplasm. The extracellular space was abundant. Astrocytic elements were found in seven of the tumors. The cells had longer and more prominent cell processes containing bundles of glial filaments. The cells in oligodendroglioma appear to preserve the ultrastructural features described by Mori and Leblond for normal oligodendrocytes. (30 Refs) (In JPN)

MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS

12. ENHANCEMENT OF HEPATOCARCINOGENESIS BY SEQUENTIAL ADMINISTRATION OF CHEMICALS: SUMMATION VERSUS PROMOTION EFFECTS.

Williams GM, Katayama S, Ohmori T
American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Carcinogenesis; 2(11):1111-1117 1981

A comparative study was made of the sequential administration of the liver carcinogen, diethylnitrosamine (DEN), or the liver tumor promoter, phenobarbital, given after the liver carcinogen, N-2-fluorenylacetamide (FAA). The effects of the second carcinogen on preneoplastic cellular lesions induced by the first carcinogen were comparable to the effects of the promoter. In addition, both sequential exposures enhanced the ultimate carcinogenic effect, although the combination of FAA followed by DEN resulted in a greater number of malignant neoplasms. Thus, enhancement of carcinogenesis by a second chemical cannot be used by itself as evidence of a promoting action. Approaches to the more precise definition of promoters include exclusion of genotoxicity, identification of epigenetic mechanisms and lack of a summation effect with administration prior to genotoxic carcinogens. (Author abstract) (50 Refs)

13. ENHANCEMENT OF EXPERIMENTAL PANCREATIC CANCER IN SYRIAN GOLDEN HAMSTERS BY DIETARY FAT.

Birt DF, Salmasi S, Pour PM
Eppley Inst. for Res. in Cancer, Univ. Nebraska Medical Center, 42d and Dewey Ave., Omaha, NE, 68105
JNCI; 67(6):1327-1332 1981

The effects of dietary fat on the induction and development of pancreatic ductular adenocarcinoma were studied in random-bred Syrian golden hamsters. Diets containing low-fat (LF) or high-fat (HF) levels of corn oil [4.5 or 18.0 g/385 kilocalorie (kcal)], contributing 10 or 41% of the cal, respectively, were fed either before or after a single injection of N-nitrosobis(2-oxopropyl)amine (BOP) (10 mg/kg body wt). Control hamsters were fed corn oil at a medium-fat (MF) level (9 g/385 kcal) for life. The incidence of ductular adenocarcinomas increased in both males and females (LF diet, 16%; HF diet, 34%) when the HF diet was fed after BOP treatment. The av number of carcinomas per carcinoma-bearing animal also increased (LF diet, 1.3; HF diet, 3.0), but the carcinoma incidence was not influenced by these diets being fed before carcinogen treatment. The incidence of ductular adenomas was high with all treatments and was not influenced by diet. However, the number of adenomas was increased in animals fed HF diets. In addition, the incidence of acinar cell nodules was elevated in animals fed the MF and HF diets after BOP administration. These results showed that dietary fat modified the development of experimental ductular adenocarcinoma of the pancreas. (Author abstract) (31 Refs)

14. COMPARISON OF THE EFFECT OF BUTYLATED HYDROXYTOLUENE ON N-NITROSOMETHYLUREA AND 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMORS.

King MM, McCay PB, Kosanke SD
Biomembrane Res. Lab., Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City, OK, 73104
Cancer Lett; 14(3):219-226 1981

The effects of butylated hydroxytoluene (BHT) on nitrosomethylurea (NMU)- and 7,12-dimethylbenz(a)anthracene (DMBA)-induced rat mammary tumors were examined. Female Sprague-Dawley rats were fed either control diets or diets plus 0.3% BHT, and further divided into NMU-treated, DMBA-treated, or nontreated groups. DMBA was administered at 10 mg in 1 ml stripped corn oil intragastrically at 50 days of age. NMU was administered at 5 mg/100 g body wt iv in the tail vein at 50 days of age. A 100% incidence of tumors was seen in rats treated with DMBA and on the control diet. The incidence was reduced to 54% by addition of BHT to the diet. No difference in tumor incidence was seen in NMU-treated animals with or without addition of BHT. The differences in tumor prophylaxis may reflect the fact that DMBA is metabolized by the monooxygenase system but NMU is not. (30 Refs)

15. EFFECT OF RETINOIDS ON THE INDUCTION OF COLON CANCER IN F344 RATS BY N-METHYL-N-NITROSOUREA OR BY 1,2-DIMETHYLHYDRAZINE.

Silverman J, Katayama S, Zelenakas K, Lauber J, Musser TK, Reddy M, Levenstein MJ, Weisburger JH
American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Carcinogenesis; 2(11):1167-1172 1981

The possible modifying effect of synthetic and natural retinoids on the incidence of colon cancer in rats induced by two intrarectal doses of 2.5 mg of N-methyl-N-nitrosourea (MNU) given once a wk for 2 successive wk or a single 150 mg/kg body weight dose of 1,2-dimethylhydrazine (DMH), sc was investigated. Emphasis was on the effect of the development of early tumors as visualized by endoscopy. With the retinoids N-ethyl-retinamide, N-2-hydroxyethylretinamide, N-(4-hydroxyphenyl)-all-trans-retinamide (RAHA) and retinyl acetate (RA) administered orally after the carcinogens, significant differences in early developing tumors were not found. At histopathological examination of the tumors the RAHA + DMH group had significantly fewer adenomas per animal. The percentage of adenoma bearing rats was significantly lower in groups receiving RAHA + DMH or RA + DMH. However, food consumption was lower in rats consuming either RAHA or RA. Retinyl palmitate (RP) and RAHA were administered intrarectally to MNU-induced rats either before or after the carcinogen. When administered before MNU, RP caused a significant increase in the percentage of tumor bearing animals and the av number of tumors per animal as visualized endoscopically. At histopathological examination, all retinoid groups except RAHA given after the carcinogen, produced significantly more adenomas per animal and a significantly greater adenoma incidence than did the control groups. Thus, in two systems, the oral administration of retinoids did not clearly inhibit the early or later stages of colon tumor development. Intrarectal infusion of two retinoids had no effect on colonic morphology but at histopathological examination of later stage tumors there was an enhanced adenoma response. (Author abstract) (36 Refs)

16. EFFECTS OF THREE RETINOIDS ON COLON ADENOCARCINOMAS, SARCOMAS AND HYPERPLASTIC POLYPS INDUCED BY INTRARECTAL N-METHYL-N-NITROSOUREA ADMINISTRATION IN MALE F344 RATS.

Wenk ML, Ward JM, Reznik G, Dean J
Microbiological Assoc., Inc., 5221 River Road, Bethesda, MD, 20816
Carcinogenesis; 2(11):1161-1166 1981

Male F344 rats, 9 wk of age, were given multiple intrarectal administrations of N-methyl-N-nitrosourea (NMU) at 0.5 mg/dose twice a wk for a total of 8, 12, or 16 doses. Five days after the final NMU instillation, rats were placed on one of four diets; chow with retinoid vehicle, chow with 654 mg N-ethylretinamide per kg diet, chow with 686 mg N-(2-hydroxethyl)retinamide per kg diet, or 406 mg retinylidene dimedone per kg diet. Groups of 40-50 rats receiving 16, 12, or 8 total doses were sacrificed 32, 44, or 52 wk after the initial NMU dose, respectively. The number of rats with colon tumors and the number of tumors per tumor bearing rat in each dosage regimen was compared to appropriate controls. Organ weights for testis, liver, and kidneys were similar for controls and retinoid treated animals and no histopathologic lesions indicative of retinoid toxicity were found. Unusual proliferative lesions of the colon in rats of all dosed groups included hyperplastic and inflammatory polyps and sarcomas. The feeding of diets containing these three retinoids did not significantly modify the incidence or multiplicity of colon tumors observed under these conditions. (Author abstract) (18 Refs)

17. THE ROLE OF AGING IN N-NITROSODIMETHYLAMINE- AND N-DIMETHYLNITRAMINE-INDUCED CARCINOGENESIS IN AMPHIBIA.

Khudolei VV
N. N. Petrov Res. Inst., Oncology USSR Ministry Health, Leningrad, USSR
Vopr Onkol; 27(10):67-71 1981

A comparison of the reactions of adult and juvenile amphibians Rana temporaria s howed that the host sensitivity (latency and tumor incidence) of both groups of animals to the carcinogenic action of N-nitrosodimethylamine and dimethylnitramine was of the same order. However, a 'shift' in organ sensitivity (different organotropic effect) was observed. The predominance of hepatocellular cancer in adult and hemocytoblastosis in young Rana temporaria was significant (p less than 0.01). The mechanisms of these 'shifts' are unknown, but a role of the metabolic and reparative processes has been suggested. (Author abstract) (18 Refs) (In RUS)

MUTAGENICITY OF NITROSO COMPOUNDS

18. COMPARATIVE NEOPLASTIC TRANSFORMATION RESPONSES OF BALB/3T3 CELLS, SYRIAN HAMSTER EMBRYO CELLS, AND RAUSCHER MURINE LEUKEMIA VIRUS-INFECTED FISCHER 344 RAT EMBRYO CELLS TO CHEMICAL CARCINOGENS.

Dunkel VC, Pienta RJ, Sivak A, Traul KA
Bureau Foods, Food and Drug Admin., Public Health Service, 200 C St., S.W., Washington, DC, 20204
JNCI; 67(6):1303-1315 1981

This study provides a preliminary comparative evaluation of the responses to a series of 49 chemicals, in in vitro transformation assays, of Balb/3T3 cells, Syrian hamster embryo cells, and Fischer 344 rat embryo cells infected with Rauscher murine leukemia virus. The chemicals assayed included aromatic amines; polycyclic aromatic hydrocarbons; alkylating agents; nitrosamines, hydrazines, and related compounds; heterocyclic compounds; amides, ureas, and acylating agents; inorganic compounds; and hormones. In all three assays 37 of the chemicals were tested. The most uniform test responses were obtained with the polycyclic aromatic hydrocarbons and inorganic compounds. With the other groups of chemicals, more variation in response was observed. This study expands the base of information on the potential of these in vitro transformation systems, and the lack of responses with some of the chemicals underscores the need for incorporation of exogenous metabolic activating systems into these assay systems. (Author abstract) (20 Refs)

19. IDENTIFYING HUMAN CELLS CAPABLE OF METABOLIZING VARIOUS CLASSES OF CARCINOGENS.

Aust AE, Antczak MR, Maher VM, McCormick JJ
Dept. Microbiology, Michigan State Univ., East Lansing, MI, 48824
J Supramol Struct; 16(3):269-279 1981

Metabolism of tritiated benzo(a)pyrene (BP) to aqueous-acetone soluble forms and inhibition of cellular DNA synthesis were used to identify human cells capable of metabolizing various classes of carcinogens. Hydrocarbon-metabolizing activity assay (HMAA) and DNA synthesis inhibition assay were optimized and the results on 15 human epithelial cell lines were compared. Four classes of carcinogens were examined: polycyclic hydrocarbons (PH), aromatic amines (AA), heterocyclic hydrocarbons, and nitrosamines. Each of the classes was activated by one or more cell lines. Cells with very low metabolizin g activity, such as NF, showed little or no cytotoxic response when exposed to BP at concentrations up to 30 uM for 48 hr. Biological results (cytotoxicity, mutagenicity, and DNA binding) suggest that the HMAA is a useful prescreen for identifying human cells that metabolize BP to biologically active forms. Cells that appeared capable of metabolizing PH or AA according to the methods were found to produce metabolites which were cytotoxic to cocultivated human xeroderma pigmentosum fibroblasts after 48 hr exposure to the carcinogen. (28 Refs)

20. A MICROSUSPENSION ADAPTATION OF THE BACILLUS SUBTILIS 'REC' ASSAY.

McCarroll NE, Keech BH, Piper CE
Dept. Toxicology, Hazleton Lab. America, Inc., 9200 Leesburg Turnpike, Vienna, VA, 22180
Environ Mutagen; 3(6):607-616 1981

Sixty-six high mw or poorly soluble compounds were tested for mutagenicity in the Bacillus subtilis 'rec' assay. Six of 13 mutagenic aromatic amines were detected as preferential inhibitors of B subtilis M45. Nine polycyclic aromatic hydrocarbons, including benzo(a)pyrene, 3-aminopyrene, 7,12-dimethylbenz(a)anthracene, and 3-methylcholanthrene, which do not elicit a genotoxic effect in Escherichia coli, were found to have preferential inhibitory activity towards M45. Anthracene, phenanthrene, and pyrene were inert. Dimethylnitrosamine and diethylnitrosamine both diminished growth of M45, as did a variety of other nitrosamines and hydrazines. The noncarcinogenic antimetabolite 5-fluoro-2'-deoxyuridine was genotoxic to M45. Acetamide, ethyl carbamate, methyl carbamate, and thiourea were inactive against M45, confirming results ob-

tained using E Coli MSA and other microbial systems. All mutagenic alkylating agents except Captan were genotoxic in M45. In contrast to results obtained in E coli, 4-nitrobiphenyl was active in the M45 system. The lack of response in E coli may result from cell wall impenetrability of the compound. The contribution of solvents to toxicity in the B subtilis and E coli MSA systems is discussed. (13 Refs)

21. ENHANCEMENT BY ELECTRON AFFINIC AGENTS OF THE THERAPEUTIC EFFECTS OF ALKYLATING AGENTS AND NITROSOUREAS AGAINST THE KHT TUMOUR: STRUCTURE-ACTIVITY RELATIONSHIPS (MEETING ABSTRACT).

Workman P, Twentyman P
MRC Clinical Oncology and Radiotherapeutics Unit, MRC Center, Hills Road, Cambridge CB2 2QH, England
Conference on Chemical Modification: Radiation and Cytotoxic Drugs, September 17-20, 1981, Key Biscayne, Florida. Committee for Radiation Oncology Studies 139 pp., 1981.

A regrowth delay assay in C3H mice was used. Misonidazole (MISO) at 2.5 n.moles/kg (equals 500 mg/kg) increased the regrowth delay for 10mg/kg lomustine (CCNU) from about 1.5 to 3.5 days, compared to about 8 days for 20 mg/kg CCNU alone. Analoges more hydrophilic than MISO, including desmethylmisonidazole, SR-2508 (iv), SR-2555 (iv), were inactive as were those with very high octanol-water partition coefficient (P) values (greater than 20). In contrast, those with P values between 0.43 and 20 tended to be more active than MISO. With 2 of the most active agents, benzonidazole (Ro 07-1051, p equals 8.5) and Ro 07-1902 (P equals 2.5), the combination with CCNU 10 mg/kg was more effective than CCNU 20 mg/kg alone. Experiments with other cytotoxics showed that 2.5-5 mmoles/kg MISO increased the effectiveness of the nitrosoureas semustine (methyl-CCNU) and carmustine (BCNU). This was also true for the nitrogen mustards cyclophosphamide and chlorambucil but not the closely related melphalan and Nitrogen mustard (HN2). (no Refs)

22. THE EFFECT OF MISONIDAZOLE OR METRONIDAZOLE PRETREATMENT ON THE RESPONSE OF THE RIF-1 MOUSE SARCOMA TO CYTOTOXIC DRUGS (MEETING ABSTRACT).

Twentyman P, Workman P
MRC Clinical Oncology and Radiotherapeutics Unit, MRC Center, Hills Road, Cambridge CB2 2QH, England
Conference on Chemical Modification: Radiation and Cytotoxic Drugs, September 17-20, 1981, Key Biscayne, Florida. Committee for Radiation Oncology Studies 139 pp., 1981.

We have studied the effect of pretreatment with either misonidazole (MISO) or metronidazole (METRO) sensitizers on the response of the RIF-1 tumor to the nitrogen mustards cyclophosphamide (CTX), melphalan (MEL), or chlorambucil (CHL), or the nitrosourea lomustine (CCNU). The sensitizers were administered ip 30 min before the cytotoxic drugs at a dose of 2.5 mmoles/kg. Both growth delay and cell survival endpoints have been used to quantitate response. The response of the tumor both to MEL and CTX was not significantly modified by either sensitizer. The RIF-1 tumor was found to be relatively insensitive to CCNU. At a CCNU dose of 45mg/kg (approx equal to the LD50), survival of clonogenic cells was only reduced to about 10% of control. Pretreatment with MISO produced a further 10-fold reduction in cell survival at this dose and also at a higher CCNU dose of 60 mg/kg. For CCNU doses of 15 to 30 mg/kg, enhancement was more variable. No enhancement of CCNU response by METRO was seen at any dose level. For CHL, cell survival curves were straight lines through the origin. Pretreatment with MISO increased the slope of the curve by a factor of 2.0 x, while the value for METRO pretreatment was around 1.5 x. Tumor growth delay caused by CHL was also increased by MISO pretreatment. At a CHL dose of 10 mg/kg, growth delays in two separate experiments were increased from 4.3 and 4.9 days to 9.8 and 9.9 days respectively. The toxicity of CHL in terms of acute LD50 is also, however, clearly increased by MISO pretreatment. (3 Refs)

23. CLONOGENIC CELL ASSAY: ANALYSIS OF HUMAN BRAIN TUMORS (MEETING ABSTRACT).

Gerosa MA, Rosenblum ML, Dougherty DV, Wilson CB
Brain Tumor Research Center, University of California, San Francisco, CA, 94143
Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 15-17, 1981, Brussels, Belgium European Organization for Research on Treatment of Cancer; 1981

Recently we developed an in vitro clonogenic assay for human brain tumors. Colonies grew from greater than 90% of primary and metastatic tumor samples cultured, and were characterized with histochemical and immunobiological methods. To date, cells from 37 tumors have been analyzed for in vitro cell sensitivity to carmustine (BCNU). A correlation between culture and clinical results was obtained for 21 samples. The predictive accuracy in 13 patients never previously treated with nitrosoureas was 70% for sensitivity and 100% for resistance, similar to results from other stem-cell assays and to the estrogen receptor assay for breast carcinoma. Problems inherent in this assay have been addressed: viable, clonogenic tumor cells representative of the cells in the solid tumor were obtained using enzyme disaggregation methods. Short-term culturing of cells increases both the colony forming efficiency and the number of cells available for drug testing, BCNU sensitivity remains the same for cultured and original cells. Effects of tumor cell heterogeneity have been evaluated by analyzing histologically distinct specimens from individual tumors. BCNU dose-response curves were generally similar among different specimens. However analysis based on single drug doses might be misleading. Analysis of data from patients harboring recurrent tumors suggests that drug delivery in situ will limit the predictive value of a sensitive response, but will not affect the predictive value of resistance. (no Refs)

CELLULAR EFFECTS OF NITROSO COMPOUNDS

24. REPAIR OF ETHYLNITROSOUREA-INDUCED DNA DAMAGE IN THE NEWBORN RAT. II. LOCALIZATION OF UNSCHEDULED DNA SYNTHESIS IN THE DEVELOPING RAT BRAIN.

Heyting C, Van't Veer L
Div. Chemical Carcinogenesis, Antoni van Leeuwenhoekhuis, The Netherlands Cancer Inst., 121, Plesmanlaan, 1066 CX Amsterdam, The Netherlands
Carcinogenesis; 2(11):1173-1180 1981

The developing rat brain is extremely sensitive to tumor induction by N-ethyl-N-nitrosourea (ENU). This sensitivity is ascribed to a defective repair of ENU-induced DNA damage. Because the different cell types of the developing rat brain are heterogeneous in their sensitivity to tumor induction, we decided to localize DNA-repair activities within this organ. In this

paper we describe the localization of carcinogen-induced unscheduled DNA synthesis (UDS). Fresh brain slices were incubated in medium containing carcinogen and [3H]thymidine, and the incorporation of tritium was detected by autoradiography. We used two carcinogens, namely ENU (a short-patch repair agent) and the long-patch repair agent N-acetox y-N-acetyl-2-aminofluorene (AAAF). Both carcinogens induced UDS in all nuclei in brains from 1-day-old rats. In brains from 10-day-old rats all neurons except the maturing granule cells of the cerebellum and the dentate gyrus had lost their capacity for ENU-induced UDS. In brains from 26-day-old rats no more neurons carried out ENU-induced UDS. The results obtained with AAAF resemble those obtained with ENU. However, neurons tend to lose their capacity for ENU-induced UDS earlier than that for AAAF-induced UDS: in brains from 10-day-old rats some of the neurons of the cerebral cortex and the thalamus were still capable of carrying out AAAF-induced UDS; in brains from 26-day-old rats AAAF-induced UDS could still be detected in some of the neurons of the thalamus. Those cells that are supposed to be sensitive to tumor induction by chemical carcinogens are still capable of carrying out ENU- as well as AAAF-induced UDS. Thus, the susceptibility of the different types of rat brain cells to tumor induction does not correlate with an inability to carry out carcinogen-induced UDS. (Author abstract) (33 Refs)

25. UNSCHEDULED SYNTHESIS OF DNA AND POLY(ADP-RIBOSE) IN HUMAN FIBROBLASTS FOLLOWING DNA DAMAGE.

McCurry LS, Jacobson MK
Dept. Chemistry, North Texas State Univ., Denton, TX, 76203
J Supramol Struct Cell Biochem; 17(1):87-90 1981

The relationship between unscheduled DNA synthesis (UDS) and poly(ADP-ribose) synthesis was examined in both normal human fibroblasts (IMR90) and in cells carrying the xeroderma pigmentosum genotype (XP12BE). Cells carrying the XP gene are repair proficient for N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). XP12BE cells were found to be grossly deficient in UV-induced UDS, while the parental XP12BE heterozygote cells showed a level of UDS similar to control cells despite the fact that the rate of conversion of NAD to poly(ADP-ribose) was 1/2 that of control cells. The presence of theophylline, an inhibitor of poly(ADP-ribose)polymerase, had no appreciable effect on UDS in normal cells induced by either UV or MNNG. No direct requirement of poly(ADP-ribose) synthesis for UDS induced by either UV or MNNG has been found, but a requirement for the removal of a specific subclass of lesions or for steps in DNA repair subsequent to UDS may exist. (22 Refs)

26. INHIBITION OF ENZYMATIC DNA METHYLATION BY N-METHYL-N-NITRO-N-NITROSOGUANIDINE IN HUMAN RAJI LYMPHOBLAST-LIKE CELLS.

Boehm TL, Drahovsky D
(c/o Drahovsky) Zentrum der Biologischen Chemie, Universitaet Frankfurt am Main, Theodor Stern Kai 7, D-6000 Frankfurt am Main 70, W. Germany
Int J Biochem; 13(12):1225-1232 1981

A single treatment of the human Raji lymphoblast-like cell line with N-methyl-N-nitro-N-nitrosoguanidine caused undermethylation of DNA which persisted in cell cycles following treatmen t. A possible relationship of such demethylation with aberrant phenotypic expression is discussed. (36 Refs)

27. STIMULATION OF TRANSFER OF METHYL GROUPS FROM O6-METHYLGUANINE IN DNA TO PROTEIN BY RAT LIVER EXTRACTS IN RESPONSE TO HEPATOTOXINS.

Pegg AE, Perry W
Dept. Physiology and Specialized Cancer Res. Center, Milton S. Hershey Medical Center, Hershey, PA, 17033
Carcinogenesis; 2(11):1195-1200 1981

An enzymatic activity present in rat liver extracts catalyzes the transfer of methyl groups from O6-methylguanine in DNA to protein. This activity was stimulated by treatment of rats with thioacetamide, carbon tetrachloride, 1,2-dimethylhydrazine, diethylnitrosamine, dimethylnitrosamine and by partial hepatectomy but not by treatment with N-methyl-N-nitrosourea or streptozotocin. These results suggest that an enhancement of this activity accompanies the increase in cell division brought about by these agents and is not necessarily a specific response to the presence of alkylated bases in DNA. (Author abstract) (38 Refs)

28. LOCAL CHANGES OF DNA STRUCTURE INDUCED BY N-METHYL-N-NITROSOUREA.

Krugliakova KE, Zhizhina GP, Smotriaeva MA
Inst. Chemical Physics, Moscow, USSR
Stud Biophys; 85(1):11-12 1981

N-methyl-N-nitrosourea (MNU) was shown to modify the structure of DNA molecule. MNU induced double-stranded and single-stranded breaks, thermolabile sites, and alkali-labile sites. The av size of MNU-induced DNA damage was 30 bases. (4 Refs) (In RUS)

29. HUMAN TUMOR STRAINS DEFECTIVE IN THE REPAIR OF ALKYLATED DNA FAIL TO REGENERATE RAPIDLY-SEDIMENTING NUCLEOIDS AFTER N-METHYL-N'-NITRO-N-NITROSOGUANIDINE TREATMENT.

Mattern MR, Paone RF, Day RS
Lab. Molecular Carcinogenesis, NIH, Building 37, 3C27, Bethesda, MD, 20205
Carcinogenesis; 2(11):1215-1218 1981

Upon treatment with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), human cell strains characterized as either proficient or defective both in repair of alkylation-damaged DNA and in supporting the growth of MNNG-treated adenovirus (Mer+ and Mer- phenotypes), all underwent a rapid relaxation of nucleoid DNA, as judged by sedimentation in 15-30% neutral sucrose gradients. DNA in the repair-proficient Mer+ strains (normal fibroblast and tumor) was restored to the rapidly-sedimenting (control) form within 2-4 hr after the removal of MNNG. In contrast, nucleoid DNA of the repair-deficient Mer- tumor strains remained slowly-sedimenting even after 48 hr of incubation. The delay recovery of Mer- nucleoid DNA was specific for MNNG damage, since after uv irradiation, to which Mer+ and Mer- strains are equally resistant, all cell lines tested underwent DNA relaxation within the 1st hr after irradiation (3 J/m(2)) and regenerated rapidly-sedimenting nucleoids within 4-6 hr of repair incubation. (Author abstract) (24 Refs)

30. THE MECHANISM OF ACTION OF 1-(2-CHLOROETHYL)-3-(METHYL ALPHA-D-GLUCOPYRANOSE-6-YL)-1-NITROSOUREA (MCNU) IN CULTURED HELA S3 CELLS.

Kanamaru R, Sato H, Asamura M, Kakuta H, Wakui A
Dept. Clinical Cancer Chemotherapy, Res. Inst. for Tuberculosis and Cancer, Tohoku Univ., Sendai-shi, Miyagi Pref. 980, Japan
Gan To Kagaku Ryoho; 8(6):877-884 1981

The mechanism of action of 1-(2-chloroethyl)-3-(methyl alpha-D-glucopyranose-6-yl)-1-nitrosourea (MCNU) was studied in cultured HeLa S3 cells. The colony formation of the cells, as an index of proliferative ability, was inhibited completely by treatment with MCNU at 200 ug/ml for 60 min and the drug concentration required for 50% inhibition was 40 ug/ml. When the cells were incubated with [14C-ethylene]-MCNU, the radioactivity bound to the acid-insoluble fraction increased linearly up to 24 hr. In contrast, when the cells were incubated with [14C-glucose]MCNU, almost no radioactivity was detected throughout the incubation period up to 24 hr, suggesting that MCNU possesses strong alkylating activity and rather weak carbamoyling activity. RNA and protein synthesis were more strongly suppressed than DNA synthesis. At 100 ug/ml and 200 ug/ml, DNA synthesis was inhibited by 75% and 90%, and RNA synthesis was inhibited by 17% and 20%, respectively, after 24 hr. Single-strand scission of DNA was observed 24 hr after treatment with 100 ug/ml for 60 min. Although marked unscheduled DNA synthesis was induced at this time, no rejoining of the damaged DNA strands occurred even after 48 hr, indicating that the last step of the DNA repair process, ligation of the nicked strand, was inhibited by the drug. Furthermore, MCNU was found to have an inhibitory effect on the processing of ribosomal RNA. (13 Refs) (In JPN)

31. STUDIES ON THE TOXICITY OF CHLORINATED P-NITROBIPHENYL ETHER. I - METHEMOGLOBIN FORMATION IN VITRO AND IN VIVO INDUCED BY NITROSO AND AMINO DERIVATIVES OF CHLORINATED BIPHENYL ETHER.

Miyauchi M, Koizumi M, Uematsu T
(c/o Uematsu) Dept. Chemical Hygiene, Hokkaido Inst. Pharmaceutical Sciences, Otaru 047-02, Japan
Biochem Pharmacol; 30(24):3341-3346 1981

Methemoglobin (Mg) formation by nitroso and amino derivatives of chlorinated biphenyl ether was investigated. The nitroso derivatives used induced Mg formation in suspensions of human RBC. Ability to induce Mg formation among the nitroso derivatives was the highest for nitrosobenzene, followed by p-nitrosobiphenyl ether, 4-chloro p-nitrosobiphenyl ether, 2,4-dichloro p-nitrosobiphenyl ether and then 2,4,6-trichloro p-nitrosobiphenyl ether. Therefore, the ability to induce Mg formation depended on the number of chlorines rather than on the position of chlorine substitution on the phenoxy group in the molecule. Since lactate decreased but glucose and xylitol increased the Mg level produced by the nitroso compounds, this reaction would appear to require an NADPH-dependent enzyme system in RBC. The amino derivatives used induced Mg formation in suspensions of human RBC with rat liver homogenates. Ability to induce methemoglobin formation among the amino derivatives was the highest for p-aminobiphenyl ether, followed by 4-chloro p-aminobiphenyl ether, 2,4-dichloro p-aminobiphenyl ether, 2,4,6-trichloro p-aminobiphenyl ether, and then aniline. After ip injection, methemoglobinemia was induced by p-aminobiphenyl ether, aniline, and 2,4-dichloro p-aminobiphenyl ether but not by 2,4,6-trichloro p-aminobiphenyl ether over the period tested. The order of Mg formation was p-aminobiphenyl ether greater than or equal to 4-chloro p-aminobiphenyl ether greater than aniline greater than or equal to 2,4-dichloro p-aminobiphenyl ether. Oral administration gave almost the same result as ip injection. The max Mg levels produced by the amino derivatives were highest for 4-chloro p-aminobiphenyl ether, followed by p-aminobiphenyl ether, 2,4-dichloro p-aminobiphenyl ether, aniline, and then 2,4,6-trichloro p-aminobiphenyl ether. However, the Mg level produced by 2,4,6-trichloro p-aminobiphenyl ether was very low and not significantly greater than the background level. (Author abstract) (35 Refs)

32. EFFECT OF 12-O-TETRADECANOYL-PHORBOL-13-ACETATE ON CA2+ EFFLUX AND PROTEIN DISCHARGE IN PANCREATIC ACINI.

Gunther GR
Dept. Biochemistry, St. Jude Children's Res. Hosp., P. O. Box 318, Memphis, TN, 38101
J Biol Chem; 256(23):12040-12045 1981

When pancreatic acini are exposed to the peptide cerulein (an analogue of the hormone cholecystokinin) or the cholinergic agonist carbamylcholine, they exhibit a rapid release of intracellular Ca++ and a rise in the level of cGMP, accompanied by discharge of secretory proteins. The phorbol ester 12-O-tetradecanoyl-phorbol-13-acetate (TPA) stimulates protein discharge without affecting the level of cGMP, while N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) elevates cGMP, but does not elicit discharge. To clarify the relationships among these events, the effect of TPA and MNNG on Ca++ efflux in guinea pig acini was determined. Cells were incubated in medium containing 45Ca++ and transferred to medium with nonradioactive Ca++ before adding the agents to be tested. Cerulein (10(-9) M), carbamylcholine (10(-5) M), and the Ca++ ionophore A23187 (5 ug/ml) all caused the release of 40-60% of the cell-associated 45Ca++ within 3 min. In contrast, acini incubated with 10(-7) M TPA, 10(-4) M MNNG, or no added agents retained over 80% of their 45Ca++ after 22 min. TPA caused significant secretory discharge within the first 15 min and did not block Ca++ efflux stimulated by other secretagogues. TPA-induced discharge requires energy and the presence of sufficient Ca++ in the extracellular medium. These observations are consistent w ith a model in which the rapid release of Ca++ into the cytoplasm triggers an increase in the level of cGMP and, by a separate series of events, protein discharge. TPA may act at a later point on the pathway to discharge, but before an obligatory step requiring Ca++. (Author abstract) (31 Refs)

IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS

33. IMMUNOGENICITY OF GUINEA PIG CELLS TRANSFORMED IN CULTURE BY CHEMICAL CARCINOGENS.

Ohanian SH, McCabe RP, Evans CH
Lab. Immunobiology, Div. Cancer Biology and Diagnosis, NCI, NIH, Public Health Service, U.S. Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 67(6):1363-1368 1981

The immunogenicity of inbred strain 2/N guinea pig fibroblasts transformed to the malignant state in vitro by chemical carcinogens was evaluated with the use of a variety of in vivo and in vitro methods including delayed-type hypersensitivity skin and tumor transplantation tests and analysis of antibody production by immunofluorescence, complement fixation, and staphylococcal protein A binding tests. Neoplastic transformation was induced by direct treatment of cells in culture with benzo[a]pyrene, 3-methylcholanthrene, or N-methyl-N'-nitro-N-nitrosoguanidine (NMMG) or by the host-mediated method by which fetuses were exposed to diethylnitrosamine or MNNG in vivo prior to cell culture. Rabbits and syngeneic guinea pigs were inoculated with unirradiated and x-irradiated clonally derived cells. Delayed hypersensitivity skin reactions to immunizing or other cells were equivalent in immunized or control guinea pigs, and no protection to tumor outgrowth from a challenge inoculum of immunizing cells was observed. Antibody activity induced in the sera of immunized guinea pigs was cross-reactive and removed by absorption with nontumorigenic cells. Rabbit antisera after absorption with fetal guinea pig cells were nonreactive with the specific immunizing or other cultured cells. Chemical carcinogen-induced neoplastic transformation of guinea pig cells can, therefore, occur without formation of detectable, individually distinct cell surface tumor-specific neoantigens. (Author abstract) (22 Refs)

EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS

34. FORMATION, OCCURRENCE, AND CARCINOGENICITY OF N-NITROSOAMINES IN TOBACCO PRODUCTS.

Hoffmann D, Adams JD, Brunnemann KD, Hecht SS
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
ACS Symp Ser; 174:247-273 1981

N-nitrosamines (NNA) formed during processing and smoking of tobacco products are discussed. Tobacco and tobacco smoke contain three types of NNA; volatile nitrosamines (VNA), NNA deriving from residues of agricultural chemicals on tobacco, and the tobacco specific nitrosamines (TSNA). VNA can be selectively reduced in cigarette smoke by cellulose acetate filter tips. The animal carcinogen nitrosodiethanolamine (NDELA) was detected in the concentrations of 0.1-6.8 ppm in tobacco and 10-40 nanog/cigarette in the smoke. NDELA induces carcinoma of the liver and kidney in rats, and carcinoma of the nasal cavity and papillomas of the trachea in hamsters. TSNA concentrations range is 1-100 ppm in tobacco and 1-10 ug/cigarette in the cigarette smoke. Reduction in tobacco smoke can be achieved by cellulose acetate filters and perforation of the filter tip. In mice, rats, and hamsters N-nitrosonornicotine is moderately active while 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone is a strong carcinogen. Carcinogenicity of N-nitrosoanatabine is under investigation. (50 Refs)

35. NUTRITIONAL ASPECTS OF CANCER PREVENTION: AN OVERVIEW.

Silverman J
American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 10595
J Am Vet Med Assoc; 179(12):1404-1409 1981

Human epidemiologic studies and supporting laboratory animal data on the relationship between nutrition and modification of cancer are reviewed. Carcinogenesis results from at least two steps: initiation and promotion. Diet, a major risk factor, can influence cancer in several ways. Food additives or contaminants can act as initiators, promoters, or inhibitors; nutritional deficiencies can cause biochemical changes. Nutritional excesses can cause metabolic changes which may then promote or inhibit cancer. A decrease in caloric intake leads to an increase in tumor latency and a decrease in the number of tumors. The incidence of breast cancer in humans is positively correlated with the consumption of animal protein, fat, and simple carbohydrates. Dietary fat also exerts a promotional effect on colonic cancer. Cancer of the prostate and pancreas is positively correlated with fat consumption, but the evidence is not absolute. Vitamin A apparently inhibits tumor formation during the promotional phase. Vitamin C does not manifest a clear protective effect against any cancer. Studies with selenium have produced disparate results, while nitrosamines have shown carcinogenicity in many species. In most cases nutrients modify rather than cause cancer. (100 Refs)

36. N-NITROSO COMPOUNDS: DIET AND CANCER TRENDS; AN APPROACH TO THE PREVENTION OF GASTRIC CANCER.

Weisburger JH
American Health Foundation, Valhalla, NY, 10595
ACS Symp Ser; 174:305-317 1981

Documented evidence for human cases of cancer unambiguously associated with short chain dialkylnitrosamines detected in foods in the Western world has not been presented yet. Other high risk regions have in common low intakes of foods with vitamin C. The risk factors for human gastric cancer include foods pickled with salt and saltpeter or residence in areas with high geochemical nitrate. Mutagenic act ivity was found for Salmonella typhimurium TA 1535 with an extract of a pickled fish frequently eaten in high risk Japan, which also induced glandular stomach cancer in rats. The formation of the mutagen can be blocked by vitamin C. In the control group (8 rats) fish extract alone was given, and no neoplastic changes in the stomach or pancreas were seen. Twelve rats were administered with extract of nitrite-treated fish. Glandular hyperplasia (6/12), squamous cell hyperplasia of the forestomach epithelium (5/12), and intestinal metaplasia was noted in this group. Several other neoplasias were noted in this group. Formation of nitrosoureido derivative can be blocked by vitamin C, vitamin E, and some other substances such as gallates. (66 Refs)

37. THE MICROECOLOGY OF GASTRIC CANCER.

Correa P, Tannenbaum SR
Dept. Pathology, Louisiana State Univ. Medical Center, New Orleans, LA, 70112
ACS Symp Ser; 174:319-329 1981

Evidence supporting the proposition that the etiologic factors of stomach cancer, operate by modifying the microenvironment of the gastric mucosa is reviewed. The progressive histological lesions of the mucosa, the altered gastric secretions, and the dietary items which apparently have an overriding influence in the gastric carcinogenesis are discussed. Observations indicate that the disease is determined mostly by the environment and not by the race of the population. The populations migrating from a high-risk area to a low-risk area keep their original high risk in the host country. The process of cancerization in the stomach mucosa seems to be a continuum of changes which turns a normal cell into a metaplastic cell and then to a progressively dysplastic cell and finally a cancerous cell. The hydrogen ion concentration (pH) and alterations in other gastric secretions (pepsinogens, blood group substances) take place in chronic atrophic gastritis. The microecology of the junction areas with high and low pH provides the unusual circumstances of having nitrate, nitrite, abundant bacteria, and a wide range of pH. High nitrite levels in the gastric cavity have been associated with the acceleration of the gastric cancer induction in experimental animals. (33 Refs)

38. VITAMIN A STATUS AND ESOPHAGEAL CANCER RISK: EPIDEMIOLOGIC AND EXPERIMENTAL EVIDENCE FOR A POSITIVE ASSOCIATION.

van Rensburg SJ, Kruger EF, Louw ME, Du Plessis JP
Natl. Res. Inst. Nutritional Diseases, P. O. Box 70, Tygenberg 7505, South Africa
Nutr Rep Int; 24(6):1123-1131 1981

To evaluate the role of vitamin A in the etiology of esophageal cancer (EC), the occurrence of EC was studied in the Transkei territory (South Africa). A moderate incidence district (9.0/100,000) was used as a low risk region and a high incidence (50.5/ 100,000) district was used as the high risk region. The survey of the dietary intake and serum levels of vitamin A showed that deficient intake of vitamin A was 1-3x more common in the low risk groups. Elevated serum values were detected in 2-4 and 6-9 yr old children from high risk group. Experiments in BD IX rats showed that the incidence of methylbenzylnitrosamine-induced EC in animals who received a diet containing 30 mg/kg of vitamin A was 2x higher than that in the animals who received a diet containing 3 mg/kg of vitamin A. The rats who received vitamin A deficient diet were free of EC. (15 Refs)

39. REDUCTION OF HUMAN EXPOSURE TO ENVIRONMENTAL N-NITROSO COMPOUNDS.

Preussmann R, Spiegelhalder B, Eisenbrand G
Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
ACS Symp Ser; 174:217-228 1981

The complex pattern of human exposure to environmental N-nitroso compounds is summarized. Recent results in three areas (N-nitrosodimethylamine in beer; volatile N-nitrosoamines in baby nipples and pacifiers; occupational exposure in the rubber industry) where significant reductions of human exposure have been achieved are presented. Of the total daily intake of N-nitrosodimethylamine (NDMA) 0.7 ug/day results from the consumption of beer. NDMA is formed during kilning of green malt. Reduction of NDMA in malt was achieved by sulfuring during the first 10 hr. Nitrosamine contamination of rubber products originates from amine-containing accelerators and stabilizers used in the vulcanization process. In W. Germany a regulation is being discussed allowing not more than 10 ppb of preformed nitrosamines and 200 ppb of nitrosatable amines in migrates of nipples and pacifiers. In a tire factory nitrosodiphenylamine was substituted by cyclohexylthiophthalimid to remove the major nitrosating agent. Peroxides as accelerators can be used to solve the nitrosamine problem. (5 Refs)

40. OCCURRENCE OF N-NITROSAMINES IN THE WORKPLACE: SOME RECENT DEVELOPMENTS.

Fine DH, Rounbehler DP
New England Inst. for Life Sciences, 125 Second Ave., Waltham, MA, 02254
ACS Symp Ser; 1740:207-216 1981

Recent data for amines, nitrosating potential, and nitrosamines are presented in the framework of assessing the extent of various human exposures to exogenous nitrosamines. Research has been concentrated on minimizing or possibly eliminating extraordinary high human exposures in industrial sector to nitrosamines. Nitrosating potential (capacity of amines to produce N-nitrosamines) of the air sample may be calibrated to the nitrogen dioxide content of the sample by passing air containing a known amount of nitrogen dioxide through a cartridge containing the marker amine. The amine content of the sample is determined by the intensity of the chemiluminescent reaction of the nitrogen oxide with ozone. Large concentrations of dimethylamine and morpholine with traces of trimethylamine, diethylamine, and triethylamine were present in air samples from a typical tire factory. After the study was initiated the level was drastically reduced to only 14 ug/ cubic meter (m3). Nitroso-dimethylamine was found in levels greater than 0.5 ug/ m3 in eight leather facilities. (9 Refs)

☆ U.S. GOVERNMENT PRINTING OFFICE : 1982—361-847/117

AUTHOR INDEX WITH CITATION NUMBERS

Adams JD..... 34
Antczak MR..... 19
Asamura M..... 30
Aust AE..... 19
Birt DF..... 13
Boehm TL..... 26
Brunnemann KD..... 34
Correa P..... 37
Day RS..... 29
Dean J..... 16
Dohy H..... 8
Dougherty DV..... 23
Drahovsky D..... 26
Du Plessis JP..... 38
Dunkel VC..... 18
Eguchi G..... 10
Eisenbrand G..... 39
Evans CH..... 33
Fine DH..... 40
Gerosa MA..... 23
Gray JI..... 1
Gregg M..... 7
Gunther GR..... 32
Hecht SS..... 34
Heyting C..... 24
Hirota T..... 9
Hoffmann D..... 34
Imaida K..... 4
Imamura N..... 8
Ito N..... 4
Jacobson MK..... 25
Kakuta H..... 30
Kanamaru R..... 30
Katayama S..... 12
Katayama S..... 15
Keech BH..... 20
Khudolei VV..... 17
King MM..... 14
Koizumi M..... 31
Kosanke SD..... 14
Koyama Y..... 9
Kruger EF..... 38
Krugliakova KE..... 28
Lauber J..... 15
Levenstein MJ..... 15
Lijinsky W..... 3
Lijinsky W..... 6
Louw ME..... 38
Maher VM..... 19
Maruyama K..... 9
Mattern MR..... 29
McCabe RP..... 33
McCarroll NE..... 20
McCay PB..... 14
McCormick JJ..... 19
McCurry LS..... 25
Mergens WJ..... 2
Miyauchi M..... 31
Musser TK..... 15
Newmark HL..... 2
Ogiu T..... 8
Ohanian SH..... 33
Ohmori K..... 9
Ohmori T..... 12
Paone RF..... 29
Pegg AE..... 27
Perry W..... 27
Pienta RJ..... 18
Piper CE..... 20
Pour PM..... 13
Preussmann R..... 39
Reddy M..... 15
Reuber MD..... 3
Reznik G..... 16
Reznik-Schuller..... 7
Rosenblum ML..... 23
Rounbehler DP..... 40
Saito O..... 8
Salmasi S..... 13
Sato H..... 30
Shirai T..... 4
Silverman J..... 15
Silverman J..... 35
Sivak A..... 18
Smotriaeva MA..... 28
Spiegelhalder B..... 39
Takahashi K..... 11
Takano T..... 4
Tannenbaum SR..... 37
Tatematsu M..... 4
Traul KA..... 18
Tsonis PA..... 10
Twentyman P..... 21
Twentyman P..... 22
Uematsu T..... 31
Ushio K..... 9
Van Rensburg SJ..... 38
Van't Veer L..... 24
Wakui A..... 30
Ward JM..... 16
Weisburger JH..... 15
Weisburger JH..... 36
Wenk ML..... 16
Williams GM..... 12
Wilson CB..... 23
Wishnok JS..... 5
Workman P..... 21
Workman P..... 22
Zelenakas K..... 15
Zhizhina GP..... 28

VIDEOTAPES

ON CURRENT TOPICS IN CANCER RESEARCH

A pilot project of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute

Three series are available . . .

THE RELATION OF CARCINOGEN ACTION ON DNA TO CELL TRANSFORMATION

PETER MAGEE Fels Research Institute	*Keynote Address*	#VK01 28 min.
JAMES K. SELKIRK Oak Ridge National Laboratories	*Metabolic Activation and Macromolecular Binding of Chemical Carcinogens*	#VK02 51 min.
PHILIP C. HANAWALT Stanford University	*Cellular Responses to Damaged DNA*	#VK03 54 min.
CHARLES HEIDELBERGER University of Southern California	*Mutagenesis and Oncogenic Transformation of Mouse Embryo Cells*	#VK04 54 min.
FRED RAPP Milton S. Hershey Medical Center	*The Interaction of Herpesviruses and Host Cells Leading to Latency or Transformation*	#VK05 52 min.
	Panel Discussion	#VK06 31 min.

MECHANISMS OF METASTASIS

ISAIAH FIDLER Frederick Cancer Research Center	*The Heterogeneous Nature of Cancer Metastasis and Implications for Therapy*	#VB01 47 min.
GEORGE POSTE Smith, Kline and French Laboratories	*Phenotypic Analysis of Metastatic Cell Populations*	#VB02 42 min.
LANCE LIOTTA National Cancer Institute	*Tumor Cell Invasion of Basement Membranes and Extracellular Matrices*	#VB03 33 min.
EVERETT SUGARBAKER Miami Cancer Institute	*Some Clinical Characteristics of Metastasis in Man*	#VB04 41 min.

AUTOMATED CYTOLOGY

Part One: Principles and Techniques		#VB05 56 min.
Part Two: Biological Applications		#VB06 52 min.

VIDEOTAPES ON CURRENT TOPICS IN CANCER RESEARCH are in the 3/4'' U-matic format and can be played on video equipment which accepts the NTSC standard (the standard for videotapes produced in the U.S.).

The videotapes are available on a loan basis. If you would like to schedule viewing for your group, or for more information, please write to:

Cancer Information Dissemination and Analysis Center (CIDAC)
Franklin Research Center
20th and Benjamin Franklin Parkway
Philadelphia, PA 19103

Please specify three choices for viewing dates, and the tapes desired.

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. CHEMICAL CARCINOGENESIS.
Farber E
Dept. Pathology, Univ. Toronto, 100 College St., Toronto, ON M5G 1L5, Canada
N Engl J Med; 305(23):1379-1389 1981

2. N-HEXANE AND ITS TOXICOLOGIC EFFECTS. A REVIEW.
Jorgensen NK, Cohr KH
Harevaenget 44, DK-4200 Slagelse, Denmark
Scand J Work Environ Health; 7(3):157-168 1981

3. SAFROLE: ITS METABOLISM CARCINOGENICITY AND INTERACTIONS WITH CYTOCHROME P-450.
Ioannides C, Delaforge M, Parke DV
Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England
Food Cosmet Toxicol; 19(5):657-666 1981

RADIATION CARCINOGENESIS

4. CARCINOGENIC, MUTAGENIC, TERATOGENIC WORKSHOP.
Suit H, Hall E, Frei E
Dept. Radiation Medicine, Massachusetts General Hosp., Boston, MA, 02114
Cancer Clin Trials; 4(Suppl):37-41 1981

5. DOSIMETRY OF THE ATOMIC BOMB SURVIVORS.
Sinclair WK, Failla P, Bond VP, Loewe WE, Kerr GD, Auxier J, Wyckoff OH, Maruyama T, Schull JW, Land EC, Dobson LR, Mays WC, Seymour J
Argonne Natl. Lab., 9700 South Cass Ave., Argonne, IL, 60439
Radiat Res; 88(3):437-447 1981

DIETARY FACTORS IN CARCINOGENESIS

6. NUTRITION AND CANCER: A REVIEW.
Muller E, Rickenbach M
Institut fur Sozial- und Praventivmedizin, Universitat Zurich, Gloriastrasse 32 B, 8006 Zurich, Switzerland
Praxis; 70(43):1903-1912 1981
In GER

7. FLAVONOIDS, MUTAGENS, AND CITRUS.
Horowitz RM
U. S. Dept. Agriculture, Agricultural Res. Service, Fruit and Vegetable Chemistry Lab., Pasadena, CA, 91106
ACS Symp Ser; 170:43-59 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. ETIOLOGICAL CONCEPTS IN CERVICAL CARCINOGENESIS.
Kessler II
Dept. Epidemiology and Preventive Medicine, Univ. Maryland Sch. Medicine, 655 West Baltimore St., Baltimore, MD, 21201
Gynecol Oncol; 12(2,part2):S7-S24 1981

9. CURRENT CONCEPTS ON THE AETIOPATHOGENESIS OF ACUTE LEUKAEMIA.
Torres A, Martinez Guibelalde F, Gomez Garcia P, Garcia Castellano JM, Manzanares Escribano MR
Jefe Servicio Hematologia, Ciudad Sanitaria 'Reina Sofia' de la Seguridad Social, Cordoba, Spain
Sangre (Barc); 26(3B):700-717 1981
In SPA

10. CANCER FAMILY SYNDROME.
Svendsen LB, Bulow S
Kirurgisk-gastroenterologisk afdeling, Bispebjerg hospital, Copenhagen, Denmark
Ugeskr Laeger; 143(42):2713-2716 1981
In DAN

11. GENETIC AND BIOCHEMICAL STUDIES WITH ATAXIA TELANGIECTASIA.
Huang PC, Sheridan RB
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205
Hum Genet; 59(1):1-9 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

12. THE HEALTH EFFECTS AND ECOLOGICAL SIGNIFICANCE OF CHLORINE RESIDUALS IN WATER.
Kalmaz EV, Kalmaz GD
Univ. Tennessee, Univ. Station 8163, Knoxville, TN, 37916
Chemosphere; 10(10):1163-1175 1981

13. CHEMICAL AND ENVIRONMENTAL AGENTS IN GASTROINTESTINAL CARCINOGENESIS.
Deschner EE, De Cosse JJ, Sherlock P
Lab. Digestive Tract Carcinogenesis, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Clin Gastroenterol; 10(3):755-771 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

14. THE REPAIR OF DNA DAMAGE: RECENT DEVELOPMENTS AND NEW INSIGHTS.
Friedberg EC, Bonura T, Love JD, McMillan S, Radany EH, Schultz RA
Dept. Pathology, Lab. Experimental Oncology, Stanford Univ., Stanford, CA, 94305
J Supramol Struct Cell Biochem; 16(1):91-103 1981

MODIFICATION OF CARCINOGENESIS

15. ROLE OF HORMONES INCLUDING DIETHYLSTILBESTROL (DES) IN THE PATHOGENESIS OF CERVICAL AND VAGINAL INTRAEPITHELIAL NEOPLASIA.
Robboy SJ, Truslow GY, Anton J, Richart RM
Dept. Pathology, Massachusetts General Hosp., Boston, MA, 02114
Gynecol Oncol; 12(2,part2):S98-S110 1981

16. PROSTAGLANDINS AND CANCER: A REVIEW OF TUMOR INITIATION THROUGH TUMOR METASTASIS.
Honn KV, Bockman RS, Marnett LJ
Dept. Biological Sciences, Wayne State Univ., Detroit, MI, 48202
Prostaglandins; 21(5):833-864 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

17. GENITAL CANCER AND VIRUSES.
Rapp F, Jenkins FJ
Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Gynecol Oncol; 12(2,part2):S25-S41 1981

18. VIRUS PAPILLOMAS IN HUMANS.
Nasemann T
Univ.-Hautklinik Eppendorf, Martinistr. 52, D-2000 Hamburg 20, W. Germany
Hautarzt; 32(11):601-606 1981
In GER

More Than Just A Fancy Name

Mention CANCERLINE to your librarian and the world's foremost collection of cancer information is at your disposal. With the help of this computerized data system, you can obtain information on the following:

Cancer Literature

The literature date base, **CANCERLIT**, allows you to survey more than 3,000 biomedical journals for information on your topic of interest. Your search will also alert you to meeting proceedings, monographs, and books published in that area. Informative abstracts averaging 200 words are provided with each citation;

Current Cancer Research

The data base **CANCERPROJ** allows you to retrieve descriptions of current work in any cancer research area. The descriptions, which state research objective, methodology, and experimental results, are supplied for projects underway in 77 countries around the world.

Cancer Therapy Protocols

The **CLINPROT** section of CANCERLINE is designed primarily for clinicians. It provides detailed summaries of currently active experimental protocols for any cancer site, agent, or type.

Ask your biomedical librarian about CANCERLINE.
CANCERLINE is sponsored by the International Cancer Research Data Bank—a program of the National Cancer Institute.

Keep Up with the Cancer Literature

Each Month
You Can Receive Abstracts
Covering Your Specialty Area

- This convenient service — called Auto SDI* — is as near as your nearest biomedical library. Discuss your research interests with the librarian who will design an appropriate search strategy.
- Abstracts of the latest published literature are searched automatically each month and those related to your interests are delivered to you on a regular basis.
- The abstracts you receive are selected from more than 4,000 monthly entries made into CANCERLIT — the extensive cancer literature data base of the National Cancer Institute.

Talk With Your Librarian
About the Auto SDI Service TODAY.

*Auto SDI stands for Automatic Selective Dissemination of Information. It is a service provided to you, at minimal cost, by the International Cancer Research Data Bank (ICRDB) — a part of the National Cancer Institute.

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
5285 Port Royal Road
Springfield, Va. 22161

OFFICIAL BUSINESS

Penalty for Private Use, $300

PRINTED MATTER

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF COMMERCE
COM-211

THIRD CLASS
BULK RATE

U.S.MAIL

CK-01

CANCERGRAMS are distributed for the International Cancer Research Data Bank (ICRDB) by the National Technical Information Service (NTIS). **CANCERGRAMS** are available from NTIS on a standing order basis at $2 each for North American Continent addressees and $3 each for other addressees. An NTIS deposit account is required. For a list of subject categories or other information, please write to:

Subscription Section
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161

NOTICE OF MAILING CHANGE

☐ Check here if you wish to discontinue receiving this publication.

☐ Check here if your address has changed and you wish to continue receiving this publication. (Be sure to furnish your complete address including zip code.)

Tear off cover with address label still affixed and send to:

Computer Support Center
ICRDB Program
IIT Research Institute
10 West 35th Street
Chicago IL. 60616

CK 01/82/06

NCI/ICRDB/CK01 82/06

PB82-935106

ICRDB CANCERGRAM

CHEMICAL CARCINOGENESIS

Nitroso Compounds

SERIES CK01 No. 82/06

JUNE, 1982

This Cancergram is a service of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM of the U.S. National Cancer Institute. Every few weeks, an updated Cancergram containing abstracts of selected cancer-related articles recently published in more than 3000 journals, and dealing with the topic indicated by the above title, is sent to researchers working in this area. These researchers are identified on the basis of the description of their current research project that has been submitted to the ICRDB Program, directly or via granting agencies.

This Cancergram is prepared by the Cancer Information Dissemination and Analysis Center (CIDAC) for Carcinogenesis Information. ***If this Cancergram is useful and valuable, please send your comments to the CIDAC address below, since future editions depend on user satisfaction and user needs:***

CIDAC FOR CARCINOGENESIS INFORMATION
SCIENCE INFORMATION SERVICES
FRANKLIN INSTITUTE RESEARCH LABORATORIES
20TH AND RACE STREETS
PHILADELPHIA, PA 19103

NEWARK PUBLIC LIBRARY

JUN 25 1982

U. S. GOVT. PUBS.
DEPOSITORY 376

SPECIAL ANNOUNCEMENTS FROM THE ICRDB PROGRAM WILL PERIODICALLY APPEAR AS FILLER PAGES IN THE BACK OF YOUR CANCERGRAMS. WATCH FOR THEM!

In this issue:

- FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS..... 1-3
- METABOLISM OF NITROSO COMPOUNDS..... 4-8
- INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS..... 9-26
- MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS..... 27-39
- MUTAGENICITY OF NITROSO COMPOUNDS..... 40-54
- CELLULAR EFFECTS OF NITROSO COMPOUNDS..... 55-65
- IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS..... 66-69
- EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS..... 70-75

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS

1. FORMATION OF NITROSO COMPOUNDS AND MUTAGENS FROM CINNARIZINE, ETHAMBUTOL, PIROMIDIC ACID, PYRIDINOL CARBAMATE AND TIARAMIDE BY DRUG/NITRITE INTERACTION.

Takeda Y, Kanaya H
Hatano Res. Inst., Food and Drug Safety Center, 729-5 Ochiai, Hadano, Kanagawa 257, Japan
Cancer Lett; 15(1):53-59 1982

The formations of nitroso compounds and mutagens from 5 nitrogen-containing drugs (cinnarizine, ethambutol, piromidic acid, pyridinol carbamate, and tiaramide) by drug/nitrite interaction were studied. The drugs (50 millimole) were reacted with nitrite (500 millimole) at pH 3.0-3.4 and 37 C for 4 hr, and the reaction mixtures were assayed for nitroso compounds and mutagens. Ethambutol, cinnarizine, and pyridinol carbamate yielded a considerable amount of nitroso compounds. The concentrations of drugs and nitrite used in the experiments were much higher than those expected to be present in the stomach after ingestion of therapeutic dosages of the drugs. Drug-nitrite interactions were examined under conditions presumed to resemble those in the stomach after ingestion of the drug to determine the possible extent of nitrosation during medication. The concentration of each drug was based on the max dose for adults and the estimated volume of the stomach content after a normal meal. The reaction product of pyridinol carbamate and nitrite was mutagenic to Salmonella typhimurium TA100 in the absence of S-9 mix. The formation of nitroso compounds was observed for ethambutol. Significant mutagenicity was detected in the reaction product of pyridinol carbamate. (15 Refs)

2. STUDY IN THE SERIES OF NITROSOUREAS: ISOMER OF (CHLORO-2 ETHYL)-1 CYCLOHEXYL-3 NITROSO-1 UREA (CCNU) AND NITROSOTHIOUREAS.

Oiry J, Martinez J, Imbach JL, Winternitz F
(c/o Imbach) Laboratoire de Chimie Bio-Organiques, Universites des Sciences et Techniques du Languedoc, Ecole Nationale Superieure de Chimie, place Eugene Bataillon, 34060 Montpellier Cedex, France
Eur J Med Chem Chim Ther; 16(6):539-543 1981

A method for the synthesis of N-alkyl N-nitrosoureas selectively nitrosated at position 3, starting with N-alkyl N-nitrosocarbamates and corresponding amines, is described. The (chloro-2 ethyl)-1 cyclohexyl-3 nitroso-3 urea isomer (CCNUi) of lomustine (CCNU) was synthesized. CCNUi and CCNU thio-analogues were less toxic than CCNU but were inactive against L1210 leukemia in mice. (15 Refs) (In FRE)

3. ANALYSIS FOR NITROSOUREA ANTITUMOR AGENTS BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY.

Smith RG, Blackstock SC, Cheung LK, Loo TL
Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Anal Chem; 53(8):1205-1208 1981

A gas chromatography-mass spectrometry assay for nitrosoureas (NUs) was described. The assay employs selected ion monitoring after derivation of the NUs with trifluoroacetic anhydride. The method was used to determine in vitro rates of decomposition of three NUs in plasma and to monitor plasma concentrations of 1-(2-chloroethyl)-3-trans-4-methylcyclohexyl-1 nitrosourea in a dog that received iv administration of 15 mg/kg. The method was selective and sensitive to low ng quantities of the nitrosoureas. (26 Refs)

METABOLISM OF NITROSO COMPOUNDS

4. METABOLIC FATE OF ASYMMETRIC N,N-DIALKYLNITROSAMINES HAVING A BUTYL GROUP IN THE RAT.

Suzuki E, Okada M
Tokyo Biochemical Res. Inst., Takada 3-14-8, Toshima-ku, Tokyo 171, Japan
Gan; 72(6):910-920 1981

The metabolic fate of N-alkyl-N-butylnitrosamines (alkyl=ethyl, propyl, and pentyl), which induce tumors in the liver and esophagus but do not induce bladder tumors, was investigated in the rat, in order to elucidate any possible correlation between metabolism and the noncarcinogenicity to the urinary bladder of these N-nitrosamines. They were extensively metabolized in the rat, no unchanged compounds being found in the urine. The metabolic pattern of these N-nitrosamines having a butyl chain was essentially similar to that of N,N-dibutylnitrosamine, which induces tumors in the bladder as well as in the liver and esophagus. They were mainly metabolized via omega-oxidation followed by beta-oxidation and/or (omega-1)-oxidation of either of the two alkyl chains. Thus the N-alkyl-N-(3-carboxypropyl)nitrosamine and/or the N-alkyl-N-(2-carboxyethyl)nitrosamine were identified as the principal urinary metabolites. Possible important factors concerned with the induction of bladder tumors by N,N-dialkylnitrosamines are discussed from the metabolic point of view. (Author abstract) (21 Refs)

5. EFFECT OF INDOLE ON N-NITROSODIMETHYLAMINE DEMETHYLASE IN RATS TREATED WITH CARBON TETRACHLORIDE.

Mostafa MH, Ruchirawat M, Weisburger EK
(c/o Weisburger) Building 31, Room 11A04, NCI, Bethesda, MD, 20205
Food Cosmet Toxicol; 19(6):717-721 1981

Carbon tetrachloride (CCl4) significantly decreased N-nitrosodimethylamine demethylase activity in Fisher rats in a dose-dependent fashion. After indole treatment, however, demethylase activity was increased, reaching a maximum after 6-12 days of indole feeding. The inhibitory action of CCl4 could be modified by indole feeding. (28 Refs)

6. TRIAZENE METABOLISM. I. THE EFFECT OF SUBSTITUENTS IN THE ARYL GROUP ON THE KINETICS OF ENZYME-CATALYSED N-DEMETHYLATION OF 1-ARYL-3,3-DIMETHYLTRIAZENES.

Godin JR, Vaughan K, Renton KW
Dept. Chemistry, Saint Mary's Univ., Halifax, N.S. B3H 3C3, Canada
Can J Physiol Pharmacol; 59(12):1234-1238 1981

A series of antitumor dimethylaryltriazenes (ArN = N-NMe2) have been studied with respect to enzyme catalyzed N-demethylation by liver microsomes and the Km values determined by Lineweaver-Burk treatment. The substituent in the aryl group of the triazene does not significantly effect the mag-

nitude of Km, which is of the same order of magnitude as the Km for aminopyrine. On the other hand, dimethyltriazenes appear to have lower Km values for demethylation than the structurally similar dimethylnitrosamines. Monomethyltriazenes, the proposed active metabolites of the dimethyltriazenes, do not undergo appreciable demethylation in the presence of microsomes and it appears that the dimethyltriazenes only demethylate once during metabolism. Spontaneous formaldehyde release from the hydroxymethyltriazene in the presence of the Nash reagent prevented an analogous study of the metabolism of these compounds. (Author abstract) (27 Refs)

7. DISPOSITION AND METABOLISM OF 1-(2-CHLOROETHYL)-3-(2',3',4'-TRI-O-ACETYL, RIBOPYRANOSYL)-1-NITROSOUREA IN RATS.

Godeneche D, Moreau MF, Madelmont JC, Duprat J, Plagne R
Unit 71, Institut National de la Sante et de la Recherche Medicale, Boite Postal 184, 63005 Clermont-Ferrand, France
Cancer Res; 42(2):525-529 1982

The antineoplastic activity in animals of 1-(2-chloroethyl)-3-(2',3',4'-tri-O acetyl,ribopyranosyl)-1-nitrosourea (RPCNU) has been widely demonstrated. The present study deals with the disposition and the metabolism in rats of three 14C-labeled species of RPCNU. The chemical plasma half-life of the drug was less than 5 min. Within the first min after injection, most of the radioactivity derived from ethyl-14C groups was recovered as volatile products. Among these, 2-chloroethanol was identified as a main component. Analysis of labeled species in urine after administration of [ethyl-14C]RPCNU showed that thiodiacetic acid and its sulfoxide were major metabolites of RPCNU (62% of the urinary radioactivity). Traces of N-acetylcarboxymethyl- and N-acetyl-hydroxyethylcysteine were also detected. The only labeled species concentrating in particular tissues was that carrying the chloroethyl moiety. Uptake to high levels of [ethyl-14C]RPCNU did occur in liver, kidney, pancreas, thymus, and Harder's gland. (Author abstract) (22 Refs)

8. STUDY OF TARGET CELLS FOR ANTINEOPLASTIC AGENT METHYLNITROSOUREA.

Sharf VG, Pulatova MK, Emanuel' NM
Inst. Chemical Physics, Moscow, USSR
Dokl Akad Nauk SSSR; 261(4):1001-1005 1981

Characteristic features of methylnitrosourea (MNU) metabolism were studied in homogenates of mouse liver. Analysis of the electron paramagnetic resonance spectra showed the formation of the nitrosyl complexes of heme proteins. These findings indicated that Hb and cytochromes are the molecular targets for reduced MNU. (6 Refs) (In RUS)

INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS

9. APPLICATION OF QUANTITATIVE STEREOLOGY TO THE EVALUATION OF ENZYME-ALTERED FOCI IN RAT LIVER.

Campbell HA, Pitot HC, Potter VR, Laishes BA
(c/o Pitot) McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Cancer Res; 42(2):465-472 1982

The mathematical science of quantitative stereology has established relationships for the quantitation of elements in three-dimensional space from observations on two-dimensional planes. This report describes the utilization and importance of such mathematical relationships for the quantitative analysis of focal hepatic lesions in terms relative to the vol of the liver. Three examples are utilized to demonstrate the utility of such calculations in the three-dimensional quantitation of hepatic focal lesions . The first is that of a computer-simulated experiment based on defined hypothetical situations. The simulations demonstrate the applicability of the computations described in this report to the evaluation of two-dimensional data from typical animal experiments. The other two examples are taken from actual experiments and involve the transplantation of hepatic cell populations into the liver of suitably prepared hosts and the quantitation of altered foci produced by initiation with diethylnitrosamine-partial hepatectomy followed by promotion with phenobarbital. These studies clearly demonstrate that the frequency and size of foci intersections viewed on two-dimensional tissue sections do not necessarily reflect the number or size of foci in the three-dimensional tissue. Only by quantitating the number and size of the foci in relation to the three-dimensional vol of the tissue can one determine the validity of the proportionality of data from two-dimensional measurements to the total number of foci per volume of tissue. Such a conclusion has important implications for quantitative studies on hepatocarcinogenesis as well as for the enumeration of premalignant lesions which occur during the natural history of carcinogenesis in any solid tissue. (29 Refs)

10. SEQUENTIAL CHANGES IN HISTOCHEMICAL LOCALIZATION OF EPOXIDE HYDROLASE AND GAMMA-GLUTAMYL TRANSPEPTIDASE DURING HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Noda K, Fukumoto Y, Oki K, Takemoto T
1st Department Internal Medicine, Yamaguchi University School of Medicine, Ube, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The subject of this study is the clarification of roles about microsomal epoxide hydrolase (EH) in promotion stage of chemical carcinogenesis. After diethylnitrosoamine (DEN) (200 mg/kg, ip), partial hepatectomy and 2-acetylaminofluorene (2-AAF) feeding (0.02%, 2 wk) were done. From 1 to 8 wk rats were sacrificed and liver tissues were fixed with ethanol. By means of peroxidase-antiperoxidase method, the changes of EH localization were studied, and also gamma glutamyl transferase (GGT) was examined by the consecutive liver tissue sections. From 2 wk the regression of EH was recognized in each focus. And in major parts of foci, GGT localized in those EH-negative areas as if in compensation. Furthermore, the change in a remodeling stage was studied with the intermittent 2-AAF feeding (0.05%) regimen. The different localization of the two kinds of marker enzymes is discussed. (no Refs)

11. HEPATOTOXIC RESPONSE OF GERMFREE RATS TO DIMETHYLNITROSAMINE (DMN) INTUBATED (MEETING ABSTRACT).

Sumi Y, Miyakawa M
Nagoya University School of Medicine, Nagoya, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 198 1, Sapporo, Japan. The Association 415 pp., 1981.

This study was designed to know whether or not gut microflora is involved in the process of the formation of hepatic lesion by DMN. Thirty-eight germfree and 60 conventional Wistar male rats were employed. DMN was intubated with

stomach tube at respective doses of 8, 9 and 10 mg/kg body wt. Forty-eight hr after the intubation, a severe liver necrosis accompanied with hemorrhage was produced at each dose in germfree rats while no such severe liver necrosis was found at each dose in conventional rats, and this result was consistent with that of tests for SGOT and SPGT, indicating that germ-free status might play a part in the augmentation of hepatic lesion by DMN. It might be concerned with difference in DMN metabolism or in immunobiological background. (no Refs)

12. HEPATOCARCINOGENICITY OF DIETHYLSTILBESTROL (DES) IN RATS (MEETING ABSTRACT).

Kamiya K, Seyama T, Kodama Y, Numoto M, Yokoro K

Department of Pathology, Hiroshima University, Hiroshima, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Despite the demonstration of carcinogenicity of DES in estrogen-susceptible tissues of some animal species, little is known about its carcinogenic effect in the liver. Castrated W/Fu rats treated with DES alone developed tumors of the liver (HT) in 30% of animals. By a combined treatment of DES and N-nitrosobutylurea (NBU) which is not hepatocarcinogen itself, HT incidence is much increased in several rat strains. In this system, androgen had no promotive effect in HT induction and the incidence correlated well with the dosage of DES. While castration prevents N-2-fluorenylacetamide (2-FAA) induced hepatocarcinogenesis, a combined treatment of 2-FAA and DES in castrated rats remarkably increased the incidence and tumor size of HT and shortened the latent period, suggesting the promotive effect of DES on the growth of transformed cells initiated by 2-FAA. Those results indicate that DES is a complete carcinogen with activities stronger in promotion than in initiation. (no Refs)

13. EARLY CHANGES OF DOG ESOPHAGEAL MUCOSA INDUCED BY N-ETHYL-N'-NITRO-N-NITROSOGUANIDINE.

Takubo K, Shisa H, Futatsuki K, Sasajima K

Dept. Pathology, Saitama Cancer Center Res. Inst., Ina-machi, Kitaadachi-gun, Saitama-ken 362, Japan

Gan; 72(6):880-885 1981

Early changes in the esophageal mucosa of dogs induced by N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) were studied. Seven 1-yr-old beagle dogs were given a solution of 250 ug ENNG/ml to drink ad libitum for 4 mo. Three different kinds of lesions (10 erosive carcinomas, 4 slightly elevated microcarcinomas and 19 leukoplakias) were recognized. These three kinds of lesions were not located adj acent to one another, and were surrounded by almost normal stratified squamous epithelium. The foci of the carcinomas revealed an abrupt transition to normal epithelium and were considered to have arisen abruptly from normal esophageal epithelium. The histogenesis of squamous cell carcinomas of the esophagus in dogs may differ from that in man. (Author abstract) (17 Refs)

14. PRODUCTION OF TUMORS IN THE UPPER G.I. TRACT OF BEAGLES BY ENNG (MEETING ABSTRACT).

Ichiki H, Tasaka K, Orima H, Kurihara M, Miyasaka K, Izumi T, Sasaki Y, Kamano T, Yasui A

Nippon Veterinary and Zootechnical College, Nippon, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Twenty home bred beagles received ethyl-N'-nitro-N-nitrosoguanidine (ENNG) with Tween 60 soln mixed with pellets for a yr (Kurihara's method). At 14 mo, melanoma on the lip of dog No 9 was resected and dog No 14 suffered from a mandibular tumor. At 15 mo, dog No 4 was sacrificed because of emaciation by laryngeal carcinoma (ca). At 20 mo, multiple polypoid tumors or ulcerative lesions of stomach were found in 17 dogs and gastric carcinoma confirmed in 12 dogs by autopsy or biopsy. Moreover, esophageal tumors were recognized in 13 dogs and 9 of them have suffered from Borr, two type ca. In this series, malignant lesions were more prominent in the mouth and esophagus than stomach, compared with previous reports by Kurihara. (no Refs)

15. THE TREATMENT OF CARCINOMA OF THE STOMACH (MEETING ABSTRACT).

Wastell C

Surgical Unit, Gordon Hospital, London SW1, England

Medicina Domani Genova '81: Ulcera Peptica e Cancro Gastrico, April 23-24, 1981, Genoa, Italy. University of Genoa 126 pp., 1981.

The only chance of cure for a patient who develops carcinoma of the stomach is complete excision of the tumor. In spite of all the advances in chemotherapy this still remains the fundamental method of treatment. It follows that results can only be improved by earlier diagnosis. Early diagnosis depends upon accurate assessment and interpretation of endoscopy, barium meal and histopathological findings obtained in response to symptoms. Generally speaking screening programmes even in populations at high risk have failed. The only other approach to early diagnosis is the attempt to recognize pre-cancerous changes in the gastric mucosa. As has been implied in the introduction, the surgical approach to these patients has been consistent over this period of time and has been directed at the complete excision of the tumor. Generally speaking the procedures performed have been radical sub-total gastrectomy. That is, removal of the part of the stomach containing the cancer, together with greater omentum, superior leaf of the transverse meso-colon, lymphnodes along the superior border of the pancreas, the nodes around the left gastric artery and the spleen. Experimental work will be described in which a rat model has been fed N-Methyl-N'-Nitro-N-Nitrosoguanidine for a period of seven mo. The stomachs were examined histologically and by special methods to distinguish neutral and acid mucins. Hyperplasia was observed as an early change in both antrum and body accompanied by increased acid mucin secretion. These findings suggest that altered mucous secretion may be a feature of early malignant change and this observation may form the basis for the very earliest detection of premalignant change occurring in the gastric mucosa. (no Refs)

16. STUDIES ON PATHOMORPHOLOGY, BIOLOGICAL PROPERTIES, AND SENSITIVITY TO ANTI-TUMOR AGENTS OF THE TRANSPLANTABLE SQUAMOUS CELL CARCINOMA (GS-742) OF MOUSE FORESTOMACH.

Lin B, Dou G, Cui Z, Sun Y, Zhang X, Li Q
Experimental Tumor Lab., Tianjin Medical Coll., Tianjin, People's Republic of China
Zhonghua Zhongliu Zazhi; 3(2):101-105 1981

Murine forestomach carcinoma cell line, GS-742, was originally induced in inbred Jinbai mice by N-methylnitrosourea; this transplantable cell line has been successfully propagated in syngeneic mice for 74 generations over a period of more than 5 yr. Its growth characteristics were stable with a graft survival rate of 100% and with no spontaneous regression; the av host survival time was about 2 mo. Pathomorphologically, this cell line was a typical squamous cell carcinoma with lymph node metastasis resembling human esophageal carcinoma. Electron microscopy showed tonofilaments and desmosomes in the cytoplasm, large intercellular spaces, and long branched microvillous structures on the cell surface. Irregular dilatation of the perinuclear cisternae and mitochondrial swelling were also observed. This cell line was shown to be quite sensitive to antitumor agents, especially to certain alkylating agents, antimetabolites and antineoplastic antibiotics. It was concluded that this cell line may serve as a useful model of esophageal cancer for anticancer drug screening and other purposes. (10 Refs) (In CHI)

17. CLINICAL AND EXPERIMENTAL STUDY OF CANCERIZATION OF COLON ADENOMA (MEETING ABSTRACT).

Kimura H, Nakamura T, Nakano G, Arai M, Hoshi H, Shoda K, Sakamoto K, Yabe M, Muratani M
First Dept. Surgery, Sch. Medicine, Gunma Univ., Maebashi-shi, Gunma Pref. 371, Japan
Program and Proceedings of the 15th Meeting of the Japanese Research Society for Cancer of the Colon and Rectum held in Kagoshima, Japan, 24 July, 1981. The Japanese Research Society for Cancer of the Colon and Rectum, Osaka Pref. 589, Japan, 66 pp., 1981.

To follow the process of cancerization from colon adenoma, clinical cases of m (carcinoma is limited to the mucosa and does not reach the submucosa) and sm (carcinoma is limited to the sub mucosa and does not reach the proper muscle) cancer and experimental colon tumors in rats were compared pathohistologically. In all 12 lesions of colon m cancer and 10 of 18 lesions of colon sm cancer (56%), adenoma was found in the same lesion. On the other hand, when 1 mg of N-methyl-N'-nitro-N-nitrosoguanidine was given daily for 30 consecutive days to male Wistar rats by rectal injection, causing an effect in 98 of the rats, there were 6 lesions of hyperplasia of the mucosa (5.2%), 55 of adenoma (47.8%), and 50 of cancer (43.4%). Most of the cancer lesions were tubular adenocarcinoma: m cancer in 23 lesions (46.0%), sm in 16 (29.6%), pm (carcinoma is limited to the proper muscle and does not extend beyond) in 8 (14.8%), and s (carcinoma is exposed to the serosal surface) in 7 (14.0%). In only four lesions of these m and sm cancers (6.8%), was adenoma found in the same lesion. Out of 55 lesions, 13 were not macroscopic protruding lesions, but small lesions consisting of some atypical tubules. In experimental colon tumors, the incidence of cancerization from adenoma was low, but very small lesions consisting of some atypical tubules were observed, and they were considered to represent a previous step in the development of polypoid adenoma. (no Refs) (In JPN)

18. A CLINICALLY RELEVANT CANINE LUNG CANCER MODEL.

Benfield JR, Shors EC, Hammond WG, Paladugu RR, Cohen AH, Jensen T, Fu PC, Pak HY, Tepiltz RL, Thoms NW
Div. Surgery, City of Hope Medical Center, Duarte, CA, 91010
Ann Thorac Surg; 32(6):592-601 1981

Applicability of a dog model for the study of lung carcinogenesis was evaluated in 28 mongrel dogs and 74 beagle dogs. Animals were subjected to endobronchial submucosal injections or topical mucosal applications of carcinogens, implantation of Silastic discs that released carcinogens at a sustained rate, application of carcinogens to the epithelium of bistomal tracheal pedicle autografts, and endobronchial implantation of 91Y-emitting capsules. The following carcinogens were used: benzo(a)pyrene, nitrosomethylurea, 7,12-dimethylbenz(a)anthracene, 3-methylcholanthrene, and 12-0-tetradecanoylphorbol-13-acetate. A total of 48 dogs survived long enough to be at risk for development of cancer. Endobronchial applications induced cancer in 17/56 lungs in 33 dogs at risk. In 14 dogs, 19 lungs remained at risk. Sustained-release implants induced 1 metastatic carcinoma in 42 lobes at risk in 15 dogs; 17 lobes in 11 dogs remained at risk. No lung cancers were detected in tracheal pedicle grafts. (19 Refs)

19. ULTRASTRUCTURAL ANALYSIS OF PANCREATIC CARCINOGENESIS. IV. PSEUDODUCTULAR TRANSFORMATION OF ACINI IN THE HAMSTER PANCREAS DURING N-NITROSO-BIS(2-HYDROXYPROPYL)AMINE CARCINOGENESIS.

Flaks B, Moore MA, Flaks A
Dept. Pathology, Univ. Bristol Medical Sch., University Walk, Bristol, England
Carcinogenesis; 2(12):1241-1253 1981

Electron and high resolution light microscope studies were made of the pseudoductular structures that develop in the pancreas of the Syrian hamster during chronic treatment with the pancreatocarcinogen, N-nitroso-bis(2-hydroxypropyl)amine (BHP). These pseudoductules, which precede the development of tumors, arise from acini, whose cells undergo dedifferentiation by selective autophagy of their zymogen granules and granular endoplasmic reticulum. It is proposed that the pseudoductules develop into the ultrastructurally similar cystic foci that appear to be the immediate precursors of pancreatic tumors in this experimental model. The possibility is discussed that the acinar cells are the primary target for BHP carcinogenesis. (Author abstract) (36 Refs)

20. SKIN TUMORS INDUCED BY PAINTING NITROSOALKYLUREAS ON MOUSE SKIN.

Lijinsky W, Winter C
Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, Frederick, MD, 21701
J Cancer Res Clin Oncol; 102(1):13-20 1981

The carcinogenic action of nitrosamides has been investigated by applying a 0.04 M solution in acetone of 17 nitrosoalkylureas and one nitrosoalkylcarbamate to the shaved intrascapular skin of female Swiss mice. Each of a group of 20 mice received 25 ul of solution twice a wk for 40 or 50 wk, after which the animals were observed until death or 100 wk. The appearance and progression of skin tumors within the painted area was charted for each animal. Nitroso-2-fluoroethylurea was toxic to the skin and was retested using a 0.01 M solution in acetone. No tumors were seen with nitrosoallylurea, nitroso-iso-butylurea, nitrosobenzylurea, and nitroso-2-phenylethylurea.

The most potent compounds were nitrosomethylurea, nitrosoethylurea, and nitroso-2-fluoroethylurea. Nitroso-n-amylurea and nitroso-n-hexylurea were somewhat less potent, each inducing tumors in 11 of 20 mice. Nitrosocarbaryl gave rise to skin tumors in eight mice. The remaining compounds, nitroso-n-propylurea, nitroso-iso-propylurea, nitroso-n-butylurea, nitroso-sec-butylurea, nitroso-n-undecylurea, nitroso-n-tridecylurea, nitrosophenylurea, and nitrosocyclohexylurea were much less effective skin carcinogens, yielding tumors in from one to five mice. No good correlation was apparent between the relative stability of the compounds, their mutagenicity to Salmonella and their carcinogenicity to mouse skin. (Author abstract) (14 Refs)

21. CARCINOGENICITY EXAMINATION OF INFLORESCENCE OF ZINGIBER MIOGA ROSCOE (MEETING ABSTRACT).

Mori H, Kato K, Hirono I, Hosaka S, Aiso S

Department of Pathology, Gifu University, Gifu, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The carcinogenicity of mioga was examined in ACI and Fisher 344 rats. In Experim ent I, a test group of ACI rats received a diet containing mioga (1 part of mioga to 2 parts of basal diet) for 365 days. The experiment was terminated 480 days after the start of feeding. In Experiment II, a test group of Fisher 344 rats received the diet of mioga throughout the experiment of 639 days. Female ACI rats in Experiment I developed significantly more urinary bladder tumors than the control group. No carcinogenic activity was observed in males in Experiment I or males and females in Experiment II. Recently, the presence of L-arginine in a methanol extract of mioga and induction of bladder carcinomas in mice with implanted pellets containing L-arginine are reported. In this study, carcinogenicity of L-arginine and possible promoting effect on bladder carcinogenesis with N-Butyl-N-(4-hydroxy butyl)nitrosamine were also examined in ACI and Fisher rats by oral administration of 0.5% L-arginine soln. However neither carcinogenicity nor promoting effect was detected in both strains. (no Refs)

22. THE CYTOTOXIC EFFECT OF ETHYLNITROSOUREA ON THE DEVELOPING RAT CEREBELLUM. MORPHOLOGIC OBSERVATIONS.

Johnson RE, Campbell RJ, Laws ER

Dept. Neurologic Surgery, Mayo Clinic and Mayo Foundation, 200 First St. SW, Rochester, MN, 55905

Acta Neuropathol (Berl); 55(4):257-261 1981

To determine the cerebellar cell population susceptible to the toxic effect of ethylnitrosourea (ENU), pregnant female or neonatal Sprague-Dawley rats were administered iv or ip injection of 240 mg/kg ENU. The animals were sacrificed 6 hr after exposure, and the cerebellum tissue was subjected to histological and electron microscope examination. Severe cytotoxic changes were observed in the external granular layer. Almost 80% of proliferating cells were lethally damaged, while the nonproliferating cells in the postmitotic premigratory zone were relatively intact. No lethal damage was observed in the internal granular layer or in the Purkinje cell layer. Electron microscope examination showed dila tation of the Golgi apparatus and accumulation of lysosomes in Purkinje cells. (20 Refs)

23. RESIDUAL DAMAGE IN HEMATOPOIETIC CELLS FOLLOWING A SINGLE DOSE ADMINISTRATION OF METHYL NITROSOUREA (MEETING ABSTRACT).

Inoue T

Department of Pathology, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

To evaluate residual damage from leukemogenic agents, capabilities of proliferation in hematopoietic stem cells (CFUs) in mice treated iv with a single leukemogenic dose (50 mg/kg body wt) of methyl nitrosourea (MNU) were examined by means of spleen colony assay, 3H-thymidine cytocide, 125 iodo-deoxyuridine incorporation into spleen and bone marrow in fatally irradiated mice transfused with 4.5 x 10(6) bone marrow cells from treated mice. Mice given MNU and kept for 3 wk were compared with a group, which had been kept for 3 days after the administration of MNU, for acute toxicity. No significant changes were observed between control and MNU-treated mice kept for 3 wk, in total bone marrow cells, number of CFUs per femur or unit number of cells, and thymidine cytocide rate of the CFUs-pool. Significant change, however, was observed in the proliferation capability of CFUs. (no Refs)

24. CYTOGENETICS OF MURINE THYMIC LYMPHOMAS INDUCED BY N-METHYL-N-NITROSOUREA: DIFFERENCE IN INCIDENCE OF TRISOMY 15 IN THYMIC LYMPHOMAS INDUCED IN NEONATAL AND ADULT MICE.

Chan FP, Ens B, Frei JV

Dept. Anatomy, Health Sciences Center, Univ. Western Ontario, London, Ontario N6A 5C1, Canada

Cancer Genet Cytogenet; 4(4):337-344 1981

Chromosome complements of murine thymic lymphomas induced by an alkylating agent N-methyl-N-nitrosourea (MNUA) were analyzed microscopically and karyotypically using the Q-banding technique. The chemical carcinogen was injected intraperitoneally into either neonatal or 7-wk-old CFW/D mice. In addition, thymic lymphomas induced in 7-wk-old AKR mice and thymic lymphomas developed spontaneously in this strain were also examined. All six lymphomas induced in neonatal CFW/D had hyperdiploid cell lines that accounted for 90% of the cells analyzed. Chromosome analysis of lymphomas induced in adult CFW/D mice showed that only four out of nine lymphomas had predominantly hyperdiploid cell lines. The remaining five lymphomas had diploid modal chromosome number although they also carried a variant line characterized by 41 chromosomes. All eight lymphomas induced in adult AKR mice and six out of seven spontaneous AKR lymphomas showed predominantly diploid modal line. The remaining spontaneous lymphoma had a hyperdiploid stem line of 41 chromosomes. Microscopic and karyotypic analysis further identified trisomy 15 as the regular chromosome abnormality in the hyperdiploid cells in lymphomas of each group, whereas cells with diploid chromosome number had no detectable chromosome abnormality. Additional trisomies were also found, but their appearance was restricted to individual tumors. Thus, the incidence of trisomy 15 in lymphomas induced by MNUA in adult CFW/D and AKR mice, as well as in the spontaneous AKR lymphomas, is significantly lower than that in lymphomas induced in neonatal mice by the same carcinogen. (Author abstract) (19 Refs)

25. EUCHROMATIN PROTEIN PHOSPHORYLATION AND NEOPLASTIC TRANSFORMATION (MEETING ABSTRACT).

DeLuca C, Smith GJ
Department of Pathology, University of New South Wales, New South Wales, Australia
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Non histone chromosomal proteins (NHCP) are thought to have a specific gene regu latory function. Identification and characterization of phosphorylated NHCP may provide useful cellular markers for the early onset of neoplasia and may elucidate mechanisms of neoplasia. The experiment design involves an analysis of euchromatin protein alteration during the initial and promotional stages of chemical carcinogenesis as outlined in the Solt-Farber regime. Diethylnitrosamine (DEN) is used as the initiating agent and promoting is achieved through the dietary administration of 2-acetylaminofluorene accompanied by a non-specific growth stimulus-partial hepatectomy. The DNAse I prepared soluble transcriptionally active (euchromatin) fraction is extracted from purified nuclei, labelled with [32P] orthophosphate in primary cell suspension culture. The chromatin proteins are analyzed by two dimensional polyacrylamide gel electrophoresis and autoradiography. Preliminary observations indicate that following a single dose of DEN (200 mg/kg ip), there is acute histological damage to nuclei at one wk and complete recovery within three wk. Electron micrographs of purified nuclei confirmed these findings. Furthermore, electrophoretic analysis of control and DEN treated animals using Coomassie blue visualization of proteins, resulted in the detection of several proteins, not evident in the control animals. (no Refs)

26. ALKYLATION OF DNA AND TISSUE SPECIFICITY IN NITROSAMINE CARCINOGENESIS.

Montesano R
International Agency for Res. on Cancer, 150, Cours Albert Thomas, 69372 Lyon Cedex 2, France
J Supramol Struct Cell Biochem; 17(3):259-273 1981

Evidence that the initiation of the carcinogenic process by nitrosamines is linked to the metabolic competence of the target tissue or cell to convert carcinogens into mutagenic metabolites, and to the binding of those metabolites to cellular DNA is reviewed. Alkylation of DNA occurs at the N-1, N-3, and N-7 positions of adenine; N-3, N-7, and O6 of guanine; N-3 and O2 of cytosine; N-3, O4, and O2 of thymine; and the phosphate groups. The initial proportion of each DNA adduct depends upon the alkylating agent. Alkylation at the oxygen atoms of DNA bases is more critical than alkylation at other positions in the mutagenesis and carcinogenesis induced by N-nitroso compounds. Tissues in which tumors occur more frequently are those in which O6-alkylguanine persists longest in DNA. The more rapid removal of O6-methylguanine from DNA of rat liver is associated with the absence of tumor production in this organ by a single dose of dimethylnitrosamine (DMN). Significant incidence of liver tumors is observed if the same dose is given 24 hr after partial hepatectomy. Data indicate that the rate of disappearance of 7-methylguanine from the liver or extrahepatic tissues is independent of DMN dose; O6-methylguanine is lost from DNA more rapidly after a low dose of DMN. The removal of O6-methylguanine from DNA can be affected by pretreating the animals with N-nitroso compounds. The modulation of DNA repair processes is discussed in relation to the tissue-specific carcinogenic effect of N-nitroso compounds. (132 Refs)

MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS

27. ENHANCEMENT OF HEPATOCARCINOGENESIS BY SEQUENTIAL ADMINISTRATION OF CHEMICALS; SUMMATION VERSUS PROMOTION EFFECTS (MEETING ABSTRACT).

Katayama S, Ohmori T, Williams GM
Department of Pathology, Osaka University Medical School, Osaka, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The enhancement of the effects of a carcinogen by a subsequently administered chemical is routinely regarded as evidence of promotion. On the other hand, as an extension of summation of multiple irreversible alterations produced by the total dose of a carcinogen, Nakahara and others have shown that sequential administration of two different carcinogens will produce a summation effect. Thus, the operational definition of a promoter based solely upon its enhancing effect in a protocol of sequential administration becomes questionable. To examine this problem, we undertook a comparison of the effects of phenobarbital (PB) versus diethylnitrosoamine (DEN) when each was given after 2-acetylaminofluorene (AAF). The effects of PB and DEN were comparable, however DEN exerted a greater enhancing effect on the oncogenic outcome of AAF exposure than PB. (no Refs)

28. SEX DIFFERENCE IN ENHANCEMENT OF GGTASE-POSITIVE FOCI BY HEXACHLOROBENZENE AND LINDANE IN RAT LIVER.

Pereira MA, Herren SL, Britt AL, Khoury MM
Health Effects Res. Lab., U. S. Environmental Protection Agency, Cincinnati, OH, 45268
Cancer Lett; 15(1):95-101 1982

The ability of hexachlorobenzene (HCB) and lindane (LN) in diethylnitrosamine (DENA) pretreated rats to enhance the incidence of gamma-glutamyltranspeptidase (GGTase)-positive foci was determined. Male and female Sprague-Dawley rats (175-225 g) were used in the experiments. HCB and LN increased the incidence of DENA and initiated GGTase-positive foci in rat liver. Animals that received a partial hepatectomy or sham operation, and then were given HCB or LN in their diet, developed relatively few GGTase-positive foci. When DENA was administered 24 hr after the partial hepatectomy, as compared to the sham operation, there was a slightly increased incidence of GGTase-positive foci. In female rats that received either a partial hepatectomy or sham operation followed by DENA, HCB and LN increased the incidence of GGTase-positive foci. In male rats, HCB and LN increased the incidence of GGtase-positive foci only when a partial hepatectomy preceded the DENA. The enhancement of GGtase-positive foci by HCB and LN was greater in female, com pared to male rats. The results suggest that hepatocarcinogenicity of HCB and LN results in tumor promotion. (33 Refs)

29. SUPPRESSIVE EFFECT OF ALUMINIUM CHLORIDE ADMINISTRATION ON MOUSE LUNG CARCINOGENESIS BY DIMETHYLNITROSAMINE.

Yamane Y, Sakai K, Ohtawa M, Murata N, Yarita T, Ide G
Faculty Pharmaceutical Sciences, Chiba Univ., Yayoi-cho 1-33, Chiba 260, Japan
Gan; 72(6):992-996 1981

The compound dimethylnitrosamine was administered to mice by ip injection once a wk for 3 wk; a high incidence of lung tumor was found 6-8 mo after the final injection. In experiment I, the incidence of mice with lung tumors was 74%, and the av number of nodules per mouse was 15.6 within 6 mo after the final injection of dimethylnitrosamine. In mice given aluminum pretreatment, these values decreased to 65% and 6.7 (p less than 0.05), respectively. In experiment II, the incidence of mice with lung tumors was 100%, and the av number of nodules per mouse was 8.7 within 7.5 mo after the final injection of dimethylnitrosamine. In mice given aluminum pretreatment, these values decreased to 79% and 4.6 (p less than 0.05), respectively. (Author abstract) (19 Refs)

30. EFFECT OF BOLANDIOL DIPROPIONATE (ANABIOL), AN ANABOLIC HORMONE, ON DIETHYLNITROSAMINE-INDUCED HEPATOCARCINOGENESIS IN RATS.

Mochizuki Y, Sawada N, Furukawa K
Dept. Pathology, Cancer Res. Inst., Sapporo Medical Coll., Nishi-17-chome, Minami-1-jo, Chuo-ku, Sapporo 060, Japan
Gan; 72(6):969-973 1981

The effect of bolandiol dipropionate (Anabiol), an anabolic steroid hormone, on hepatocarcinogenesis was investigated in rats. Anabiol was injected at a dose of 5 mg into the thigh muscle at intervals of 2 wk, simultaneously with or subsequently to the 4-wk administration of diethylnitrosamine (DEN). The average number of tumors larger than 3 mm in diameter per rat in the subsequently treated group at 25 wk after commencement of DEN was significantly increased and the number of tumors larger than 5 mm in diameter per rat in the simultaneously treated group was significantly increased, when compared with that in the group given DEN alone. Thus, the enhancing effect of Anabiol on hepatocarcinogenesis was evident in terms of tumor size, regardless of whether the hormone was given simultaneously with or subsequently to the carcinogen. (Author abstract) (24 Refs)

31. EFFECT OF DISULFIRAM ON THE TOXICITY AND CARCINOGENICITY OF N-METHYL-N-NITROSOBENZYLAMINE IN RATS.

Schweinsberg F, Burkle V
Hygiene-Institut, Universitat Tubingen, Silcherstr. 7, D-7400 Tubingen, W. Germany
J Cancer Res Clin Oncol; 102(1):43-47 1981

The concurrent application of disulfiram (710 mg/kg diet; or 200 mg/kg diet) effects a strong enhancement of the toxicity and an acceleration of the formation of esophageal tumors by N-meth yl-N-nitrosobenzylamine (10 mg/l drinking water) in female SIV 50 rats. Besides that squamous cell papilloma in the trachea and extended squamous cell metaplasia in the bronchus system with potentially but not safely precancerous nature were seen. (Author abstract) (10 Refs) (In GER)

32. CIRCADIAN VARIATION IN THE SUSCEPTIBILITY OF MOUSE EPIDERMIS TO CHEMICAL CARCINOGENS.

Iversen OH, Kauffman SL
Inst. Pathology, Univ. Oslo, Rikshospitalet, Oslo 1, Norway
Int J Chronobiol; 8(1):49-62 1981

Groups of hairless mice were given a single topical application of each of two highly-reactive carcinogens (methylnitrosourea and beta-propiolactone) at 12(00) and 00(00). The tumor yield was as follows: for methylnitrosourea there was a slightly higher yield of skin tumors in the animals painted at 12(00); for animals painted with beta-propiolactone, there was a significantly higher skin tumor yield in those painted at 12(00). When the groups painted with the two carcinogens are considered together, there was a significantly higher number of animals with all types of tumors in the group painted at 12(00). Hence, there seems to be a circadian variation in the sensitivity of a tissue to a single contact with a chemical carcinogen. This may be related to the proliferative state of the tissue involved: at 12(00), DNA and cell division takes place at a more rapid rate than at 00(00). (Author abstract) (30 Refs)

33. EFFECT OF PHENOBARBITAL, POLYCHLORINATED BIPHENYL AND SODIUM SACCHARIN ON HEPATIC AND RENAL CARCINOGENESIS IN UNILATERALLY NEPHRECTOMIZED RATS GIVEN N-ETHYL-N-HYDROXYETHYLNITROSAMINE ORALLY.

Hirose M, Shirai T, Tsuda H, Fukushima S, Ogiso T, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Carcinogenesis; 2(12):1299-1302 1981

The effects of phenobarbital (PB), polychlorinated biphenyl (PCB) and sodium saccharin (SS) on hepatic and renal carcinogenesis induced by N-ethyl-N-hydroxyethylnitrosamine (EHEN) were examined in male F344 rats. The rats were given 0.1% EHEN in their drinking water for 2 wk and then diet containing 0.05% PB, 0.05% PCB or 5% SS for 32 wk. In wk 3, the right kidney was removed to promote renal neoplasia. The incidence of hepatocellular carcinoma was much higher in rats given PB or PCB than in controls given EHEN alone. PB administration significantly decreased the av number of renal-cell tumors per unit area and SS reduced the numbers of early neoplastic nodules. Treatment with PCB had no effect on renal carcinogenesis. These results indicate that chemicals may have either a promotive or inhibitory effect depending on the organ. (Author abstract) (25 Refs)

34. EFFECT OF PHENOBARBITAL ON CHEMICALLY-INDUCED NEOPLASMS, MALFORMATIONS AND DOMINANT LETHALS IN MICE (MEETING ABSTRACT).

Gotoh H, Nomura T, Shibata K, Hata S, Enomoto T, Kusafuka T, Miyamoto S, Sakamoto Y
Department of Fundamental Radiology, Osaka University School of Medicine, Osaka, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Phenobarbital (40-80 ug/g, sc) pretreatment of young adult and adult ICR/Jcl mice greatly diminished lung tumorigenesis initiated by urethane, furylfuramide (AF-2), and 7,12-dimethylbenz(a)anthracene (DMBA), while phenobarbital pretreatment enhanced embryo toxicities initiated by urethane, dimethyl-nitrosamine, 4-nitroquinoline-1-oxide, AF-2, and aminopyrine, but did not affect x-ray-induced ones. DMBA-induced dominant lethals were also enhanced by phenobarbital pretreatment. (no Refs)

35. ENHANCED INHIBITION OF MAMMARY CARCINOGENESIS BY COMBINED TREATMENT WITH N-(4-HYDROXYPHENYL)RETINAMIDE AND OVARIECTOMY.

McCormick DL, Mehta RG, Thompson CA, Dinger N, Caldwell JA, Moon RC

Lab. Pathophysiology, Life Sciences Div., IIT Res. Inst., Chicgo, IL, 60616

Cancer Res; 42(2):508-512 1982

Bilateral ovariectomy and dietary administration of the retinoid N-(4-hydroxyphenyl)retinamide (4-HPR) are both effective inhibitors of chemical carcinogenesis in the rat mammary gland. The present study was designed to determine whether an enhanced inhibitory effect is obtained with combined ovariectomy and 4-HPR administration, compared to either treatment alone. In separate experiments, 50-day-old virgin female Sprague-Dawley rats received either a single iv injection of 50 mg N-methyl-N-nitrosourea per kg body wt or a single intragastric dose of 20 mg 7,12-dimethylbenz(a)anthracene. The experimental design was the same in both the N-methyl-N-nitrosourea and 7,12-dimethylbenz(a)anthracene experiments: Group 1, 25 intact rats, placebo diet; Group 2, 25 intact rats, supplement of 782 mg 4-HPR per kg diet; Group 3, 50 ovariectomized rats, placebo diet; Group 4, 50 ovariectomized rats, supplement of 782 mg 4-HPR per kg diet. Feeding of the 4-HPR supplement was begun 7 days after carcinogen administration; ovariectomy was performed 7 days post-7,12-dimethylbenz(a)anthracene or 14 days post-N-methyl-N-nitrosourea. In both experiments, combined ovariectomy plus 4-HPR was significantly more active in suppressing mammary cancer induction than was either manipulation alone. 4-HPR was a more effective inhibitor of carcinogenesis in ovariectomized rats than in intact animals. These data indicate that 4-HPR is highly effective in inhibiting ovarian hormone-independent cancers and suggest that retinoid inhibition of mammary carcinogenesis does not involve an influence on ovarian hormone action. (Author abstract) (19 Refs)

36. ENHANCING EFFECT OF VAGOTOMY AND PYLOROPLASTY ON GASTRO-INTESTINAL NITROSAMIDE-I NDUCED CARCINOGENESIS IN HAMSTERS (MEETING ABSTRACT).

Mori H, Domellof L, Weisburger JH, Williams GM

Department of Pathology, Gifu University, Gifu, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The possible promoting effect of vagotomy and pyloroplasty on N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) induced carcinogenesis in the gastrointestinal (GI) tract was studied in Syrian golden hamsters on a high fat diet. After truncal vagotomy and pyloroplasty (Group 1) or sham operation (Group 3), 50 ug/ml of MNNG was given for 4 mo in drinking water. Similarly operated (vagotomy + pylorplasty) (Group 2) or non-operated (Group 4) animals without carcinogen administration served as controls. Spindle cell sarcomas of the stomach and small intestine as well as spindle cell proliferation occurred frequently in the MNNG treated hamsters (Groups 1 and 3). A small number of hamsters in Group 1 also developed adenocarcinomas and rosette-forming tumors in GI tracts. Statistically, a significantly higher incidence of tumors of the GI tract or glandular stomach was noted in Group 1 compared to Group 3. The results suggest that this operation has an enhancing effect on the MNNG carcinogenicity in the hamster. (no Refs)

37. ENHANCING EFFECT OF URINE ON BLADDER CARCINOGENESIS BY MNU (MEETING ABSTRACT).

Miyata Y, Babaya K, Oyasu R

Department of Pathology, Northwestern University Medical School, Chicago, IL

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

It has been firmly established that urine plays an important role in urinary bladder carcinogenesis. Using a heterotopically transplanted rat bladder (HTB), we have demonstrated that normal urine has a tumor enhancing effect on bladder carcinogenesis. In that study, however, the bladder epithelium was exposed to carcinogen in the presence of urine, and possible involvement of urine in the initiation step could not be ruled out. The present investigation was conducted with 2 major goals in mind: 1) to remove the possible effect of urine during the initiation step, and 2) to establish a model system where potential modifiers of bladder carcinogenesis may be tested. Young male Fisher rats, 4 wk post transplant, were divided into 6 groups. For the first 2 groups, 0.25 mg of methyl-1-nitrosourea (MNU) was instilled directly into HTB once a wk 3 x. A wk after the last dose, one half of rats received normal rat urine into HTB (group 1), and the other half 0.9% saline (group 2) weekly. The second 2 groups of rats received a single dose of MNU, and subsequently urine (group 3) or saline (group 4). Groups 5 and 6 rats served respectively as urine and saline controls without prior exposure to carcinogen. The bladder cancer incidences in HTB's are as follows: group 1, 16/18; group 2, 6/18; group 3, 14/23; group 4, 2/22; group 5, 1/19; and group 6, 0/18. The results indicate urine plays an enhancing role in the bladder where epithelial cells are initiated by carcinogen in the urine-free environment. The schedules established above may be useful to test the role of modifiers of carcinogenesis. (1 Ref)

38. INDUCTION OF RAT COLONIC EPITHELIAL ORNITHINE DECARBOXYLASE (ODC) BY BILE SALTS, AND ITS ENHANCEMENT BY COLON CARCINOGENS PRETREATMENT (MEETING ABSTRACT).

Takano S, Akagi M, Bryan GT

Department of Surgery, Kumamoto University, Kumamoto, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

A single intrarectal (ir) instillation of bile salts, presumptive colon promoters, results in a significant, early transient dose-response induction of rat colonic polyamine biosynthetic enzymes, ODC and S-adenosyl-L-methionine decarboxylase. Pretreatment by ir N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) or sc dimethylhydrazine (DMH) 1 wk before bile salt treatment enhanced and prolonged deoxycholate-induced ODC levels. This enhancement was dependent on pretreatment dose of MNNG, and was observed up to 3 mo after MNNG pretreatment. These data suggest that induced colonic ODC activity by bile salts may be related to colon carcinogenesis in a manner analogous to that shown to occur in mouse skin tumor systems. (no Refs)

39. ANTI-TUMOR EFFECT OF SYNGENEIC SPLEEN CELLS TREATED WITH IMMUNE RNA AND TUMOR ANTIGEN.

Fukushima M, Colmerauer ME, Nayak SK, Koziol JA, Pilch YH
(c/o Pilch), Univ. Hosp.-H891B, 225 Dickinson St., San Diego, CA, 92103
Int J Cancer; 29(1):113-117 1982

The antitumor effect of syngeneic spleen cells, xenogeneic immune RNA (I-RNA) and tumor antigen (TA) was studied in a chemically induced (N-methyl-N-nitrosourethane) colon carcinoma model in BALB/c mice. When the mice were treated, sequentially, with these three elements by local injection under the tumor, complete tumor regression was observed in 25% of the animals. Complete tumor regression was observed in 17% of animals treated by injection of spleen cells pre-incubated with I-RNA in vitro followed by an injection of TA. When spleen cells were treated first with I-RNA and then with mitomycin-C, therapeutic benefit was obtained and the survival rate of mice treated with these spleen cells and TA was significantly higher than that of the control group (no treatment). The antitumor effect of this treatment was abrogated completely when spleen cells were treated with mitomycin-C prior to I-RNA incubation. When spleen cells were incubated with TA in vitro or after incubation with I-RNA and then injected into tumor-bearing mice, no antitumor effect was noted. These data suggest that DNA synthesis and/or lymphocyte proliferation is essential for the action of I-RNA in sensitizing lymphocytes but not essential in the interaction of I-RNA-sensitized lymphocytes with TA. In addition it appeared that, under the conditions used, the participation of host factors was essential in the latter interaction, since treatment of I-RNA-sensitized lymphocytes with TA in vitro was ineffective. (Author abstract) (13 Refs)

MUTAGENICITY OF NITROSO COMPOUNDS

40. INTERINDIVIDUAL VARIATION OF CARCINOGEN ACTIVATION BY HUMAN LIVER HOMOGENATES: A STUDY USING DIMETHYLNITROSAMINE (DMN) AND CYCLOPHOSPHAMIDE (CP) AS PRECURSOR GENOTOXIC AGENTS AND CLASTOGENICITY AND INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER V79-E CELLS AS ENDPOINTS.

Thust R
Res. Group Preventive Oncology, Inst. Pathology, Medical Acad. Erfurt, Nordhauser Str. 74, DDR-5060 Erfurt, E. Germany
Arch Geschwulstforsch; 52(2):97-104 1982

Interindividual variation in activation of carcinogens by liver homogenates (LH) from six kidney donors was studied. Liver tissue was homogenized and centrifuged at 9,000 gravities. Similar LH were made from livers of inbred rats of strain E. Mixtures of LH supernatants (S-9) and exponentially growing, asynchronous Chinese hamster V79-E cells were exposed to dimethylnitrosamine (DMN) or cyclophosphamide (CP) for 3 hr. Human S-9 alone produced no abnormalities in V-79-E cells. With 10(-2) DMN human S-9 produced 43.7% abnormal metaphases (AM), with a 1.3-fold variation among individuals; 3.46 sister chromatid exchanges (SCE)/chromosome were produced, with a 1.3-fold variation. With the same level of DMN, rat S-9 produced 35% AM and 3.53 SCE/chromosome. With 10(-3) M CP human S-9 produced AM ranging from background levels to complete cell killing; SCE ranged from 1.33-7.35/chromosome. With 10(-4) M CP, rat S-9 produced 16% AM and 2.82 SCE/chromosome. With 10(-3) M CP, rat S-9 produced total cell killing. Results indicate that human LH activate DMN to approx the same extent as rat LH, but that activation of CP by human LH is much more varied. (33 Refs)

41. INDUCTION OF SISTER CHROMATID EXCHANGES IN HUMAN DIPLOID FIBROBLASTS BY MUTAGENS WITH AND WITHOUT RAT LIVER MICROSOMAL ACTIVATION.

Yang DP, Graupensperger F, Minecci LC, Rubin BA
Wyeth Laboratories, Inc., PO Box 8299, Philadelphia, PA, 19101
Environ Mutagen; 3(1):45-52 1981

Effects of a promutagen, a plant clastogen, and two direct mutagens were tested on sister chromatid exchange (SCE) induction in WI-38 cells with and without rat liver microsomal activation. Exponentially growing cells, 24 hr after subcultivation were treated with cyclophosphamide (CY), maleic hydrazide (MH), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), and 4-nitro-quinoline-1-oxide (4NQO) at various concentrations in the growth medium at 37 C for 1 hr. The frequency of SCE was estimated by the 5-bromodeoxyuridine-dye technique with and without addition of rat liver microsomal suspension (S-9). CY concentrations from 1 x 10(-5) M to 1 x 10(-3) M with S-9 mix increased the number of SCE/cell in a dose-dependent manner. Without S-9 mix, CY concentrations less than 1 x 10(-3) M did not produce more SCE than the controls. MNNG at 1 x 10(-8) M and 4NQO at 1 x 10(-7) M without S-9 produced significant increases in SCE/cell. Addition of S-9 slightly decreased the effects of MNNG and 4NQO in the formation of SCE. MH was tested at pH 6.4 and pH 7.6. MH at 1 x 10(-3) M without S-9 mix inhibited cell multiplication at pH 7.6, but did not cause a significant increase in SCE/cell. No interactions were noted between MH (2 x 10(-4) M) and S-9 mix nor between MH and pH levels tested. Results indicate that in the presence of metabolic activation, SCE formation in human diploid fibroblasts in vitro may be used as a potential assay for mutagenicity. (35 Refs)

42. ISOLATION AND PARTIAL CHARACTERIZATION OF MUTAGEN-SENSITIVE AND DNA REPAIR MUTANTS OF CHINESE HAMSTER FIBROBLASTS.

Schultz RA, Trosko JE, Chang CC
(c/o Trosko) Dept. Pediatrics and Human Development, Coll. Human Medicine, Michigan State Univ., East Lansing, MI, 48824
Environ Mutagen; 3(1):53-64 1981

Isolation and partial characterization of several mutants of Chinese hamster cells, which are affected in their ability to repair DNA damage or in their sensitivity to radiation or chemical mutations, are discussed. Cells of a subclone of the V79 aneuploid cell line were mutagenized by combined treatment with 5-bromodeoxyuridine and blacklight, followed by UV irradiation. 3H-thymidine was incorporated in repair-proficient cells at high temperature (38.5 C) following UV damage. Cells were held in the cold (4.0 C) to induce radioactive thymidine killing. Repair-deficient and UV-sensitive cells which had survived and formed colonies at low temperature (34.0 C) were tested for recovery. Seventy-two surviving colonies were isolated from 2 x 10(7) cells plated for selection. Four colonies were selected for extensive study. Colony UVs-7 was slightly more sensitive to UV, but not sensitive to x-rays or N-acetoxy-2-acetylaminofluorene (NAc-AAF); this mutant exhibited a highly reduced level of unscheduled DNA synthesis (UDS), as compared to the parental line. UVs-40 and UVs-44 line colonies were sensitive to UV, x-ray, N-methyl-N-nitro-N-nitroso-

guanidine, and NAc-AAF, but exhibited normal UDS. Line UVr-23 had enhanced UDS, was resistant to UV, but exhibited no difference in sensitivity to x-ray or NAc-AAF. These four mutants are all stable, and may be useful for the study of mammalian DNA repair processes and mechanisms of mutagenesis. (38 Refs)

43. CHEMICALLY-INDUCED UNSCHEDULED DNA SYNTHESIS IN PRIMARY RAT HEPATOCYTE CULTURES: A COMPARISON WITH BACTERIAL MUTAGENICITY USING 218 COMPOUNDS.

Probst GS, McMahon RE, Hill LE, Thompson CZ, Epp JK, Neal SB
Div. Toxicology, Lilly Res. Laboratories, Greenfield, IN, 46140
Environ Mutagen; 3(1):11-32 1981

Hepatocyte primary culture (HPC)-DNA repair test using a relatively large number of compounds representing a wide variety of chemical classes is discussed. Over 200 compounds were tested for induction of unscheduled DNA synthesis (UDS) and the results were correlated with bacterial mutagenicity using a modified Ames test. A positive response was seen in both systems with many procarcinogens and ultimate carcinogens while compounds believed to be noncarcinogens were inactive. Recognized carcinogens/mutagens were readily detected by the two systems. Structurally related noncarcinogens produced negative results in both systems. The modified Ames test and the HPC-UDS repair test were sensitive to compounds capable of interacting with DNA, and represent acceptable tests for genotoxic substances. The induction of UDS in hepatocytes showed good correlation with bacterial mutagenesis in response to polycyclic aromatic hydrocarbons, aromatic amines, biphenyls, nitrosamines, carbamates, azo-compounds, acridines, halogenated compounds, nitrosoureas, quinolines, pyridines, purines, pyrimidines, esters, and carbamates. Nitrocompounds although active in bacteria, were poor inducers of UDS. Results support the complementary and confirmatory nature of the tests for genotoxic chemicals and indicate the usefulness of the hepatocyte UDS system as a component in a battery of short-term predictive tests for mutagens/carcinogens. (45 Refs)

44. DNA-DAMAGING ACTIVITY IN VIVO AND BACTERIAL MUTAGENICITY OF SIXTEEN AROMATIC AMINES AND AZO-DERIVATIVES, AS RELATED QUANTITATIVELY TO THEIR CARCINOGENICITY.

Parodi S, Taningher M, Russo P, Pala M, Tamaro M, Monti-Bragadin C
Dept. Oncology, Genoa Univ., Genoa, Italy
Carcinogenesis; 2(12):1317-1326 1981

Sixteen aromatic amines and azo-derivatives were studied. They were: benzidine; 2-acetylaminofluorene; 3'-methyl-p-dimethylaminobenzene; o-aminoazo-toluene; p-dimethylaminoazobenzene; 2,4-diaminotoluene; 4,4'-oxydianiline; 2,4-diaminoanisole; 4,4'-methylenedianiline; 2-naphthylamine; Auramine O; Rhodamine B; Ponceau MX; 1-naphthylamine; p-aminoazobenzene and aniline. The compounds were examined for their capability to induce alkaline DNA fragmentation in rat liver after treatment in vivo, for their mutagenicity in the Salmonella strains TA 98 and TA 100, for their acute toxicity and for their carcinogenicity in mice and rats. For each parameter a quantitative potency index was established, and the correlation existing amongst the different parameters investigated. Only mutagenicity in the strain TA 98 was sli ghtly correlated with carcinogenic potency (r = 0.408). DNA fragmentation and toxicity were not correlated with carcinogenicity. A significant correlation was found between DNA fragmentation and toxicity (r = 0.539). No correlation was found between DNA fragmentation and mutagenicity. The lack of correlation between DNA fragmentation and carcinogenicity is in contrast with previous results obtained with a family of hydrazine derivatives and a group of nitroso compounds. For these two groups of chemicals correlation between DNA fragmentation and carcinogenicity existed, but not between carcinogenicity and mutagenicity in the Ames' test. It is suggested that short term tests can perform very differently for different classes of chemicals. (Author abstract) (22 Refs)

45. A CORRELATION BETWEEN MUTAGENIC AND CARCINOGENIC POTENCIES IN A DIVERSE GROUP OF N-NITROSAMINES: DETERMINATION OF MUTAGENIC ACTIVITIES OF WEAKLY MUTAGENIC N-NITROSAMINES.

Lee SY, Guttenplan JB
(c/o Guttenplan) Dept. Biochemistry, New York Univ. Dental Center, New York, NY, 10010
Carcinogenesis; 2(12):1339-1344 1981

The mutagenic activities of a diverse group of N-nitrosamines were measured in Salmonella typhimurium TA 100 under conditions designed to maximize metabolism of N-nitrosamines and enhance their mutagenic effects. These conditions were also chosen since some of the carcinogens were previously reported to be non-mutagenic or of questionable mutagenic activity and some only became mutagenic after the bacteria were exposed to a 'threshold dose' of metabolites. The mutagenic potencies spanned a range of 10(5)-fold and correlated well with semiquantitative carcinogenic potencies taken from the literature. This correlation appears to be the strongest yet reported for any particular class of compounds. In addition, the mutagenic activities of a number of carcinogens, previously reported to be non-mutagenic, were determined. Among the structural features necessary for high mutagenic activity in this group of compounds was a potential, unsubstituted methylating or ethylating group. Substitution of alkyl, hydroxyl methoxyl, and cyano moieties at the alpha or beta carbon of these groups reduced mutagenic activity. (Author abstract) (34 Refs)

46. METABOLIC ACTIVATION OF CARCINOGENS IN THE SALMONELLA MUTAGENICITY ASSAY BY HAMSTER AND RAT LIVER S-9 PREPARATIONS.

Raineri R, Polley JA, Pienta RJ, Andrews AW
Chemical Carcinogenesis Program, Fredrick Cancer Res. Center, Frederick, MD, 21701
Environ Mutagen; 3(1):71-84 1981

In the Salmonella mutagenicity assay, mutagenicity of the known carcinogens 2-acetylaminofluorene (AAF), 2-aminoanthracene (AA), 3-methylcholanthrene (MCA), benzo(a)pyrene (BP), and diethylnitrosamine (DEN) were directly compared using either uninduced or phenobarbital (PB)- or Aroclor (AC)- induced liver S-9 preparations from both male and female hamsters and rats. Effects of different concentrations of the S-9 protein were studied. Mutagenicity data were compared with the aryl hydrocarbon hydroxylase (AHH) and BP-4,5-epoxide hydrase (EH) activities of the liver S-9 preparations, and the levels of binding of BP metabolites to DNA were measured. The preparations from hamster liver were consistently more effective than those from rat liver for the activation of AAF, AA (except for AC-induced preparations), MCA, and DEN to their mutagenic forms. Induced preparations from rats were more active than those from hamsters when using BP. With the aromatic amines (AAF and

AA), a partial inhibition of mutagenicity occurred at the highest protein concentrations tested. Inverse relationship was observed with BP between protein concentration and number of revertants occurring in the presence of the preparation from PB- and AC-induced male and female rats. Relative order of activities of AHH and EH in preparations was AC-induced greater than PB-induced greater than uninduced. An exception was the liver S-9 preparation from AC-induced female rats, which induced no EH activity. Levels of binding of the metabolites of tritiated BP to calf thymus DNA were correlated with AHH levels except in the case of the preparation from PB-induced female rats, in which no binding was detected. (31 Refs)

47. USE OF A RAT/HAMSTER S-9 MIXTURE IN THE AMES MUTAGENICITY ASSAY.

Weinstein D, Katz M, Kazmer S
Hoffmann-La Roche Inc., Bldg. 100, Nutley, NJ, 07110
Environ Mutagen; 3(1):1-9 1981

Mutagenicity of phenacetin, 2-aminoanthracene (2AA), 1,2-epoxybutane, and nitrosopiperidine was tested using liver S-9 from Sprague-Dawley male rats and male Syrian golden hamsters. Prior studies with phenacetin have shown that the standard Ames test induced with rat S-9 is negative, while with hamster S-9 it is positive. The use of a mixture of rat and hamster liver homogenates does not inhibit the ability to cause a mutagenic effect with phenacetin. The effectivness of rat S-9 to activate low concentrations of 2AA to mutagenicity for strains TA 1535, TA 100, and TA 1537 is not inhibited by mixing with hamster S-9. 2AA concentration of 0.10 ug/plate was mutagenic with rat S-9 alone or the mixture for strains TA 1535, TA 100, and TA 98. A low concentration of 0.25 ug/plate with strain TA 1537 was also mutagenic with rat S-9 alone or the mixture. The mutagenicity of the weak mutagen epoxybutane is similar with rat S-9 and rat/hamster S-9. The mixture causes more pronounced mutagenicity by nitrosopiperidine than rat S-9 alone. The mixture was comparable to the rat S-9 alone indicating that replacing rat S-9 with a rat/hamster S-9 mixture in the standard Ames test could increase the sensitivity of the test without interfering with rat S-9 activity. (18 Refs)

48. MUTAGENICITY OF 4-AMINOAZOBENZENE, N-HYDROXY-4-AMINOAZOBENZENE, 4-NITROSOAZOBENZENE, 4-NITROAZOBENZENE, AND THEIR RING METHOXYLATED DERIVATIVES ON SALMONELLA.

Hashimoto Y, Watanabe HK, Degawa M
Dept. Hygienic Chemistry, Pharmaceutical Inst., Tohoku Univ., Aobayama, Sendai 980, Japan
Gan; 72(6):921-929 1981

The mutagenicity of 4-aminoazobenzene (AAB), N-hydroxy-4-aminoazobenzene, 4-nitroazobenzene, and their 2-, 3-, 4'-methoxyl and 2,5-dimethoxyl derivatives, and 2-methoxy-4-nitrosoazobenzene and 3-methoxy-4-nitrosoazobenzene were examined on Salmonella typhimurium TA98 and TA100. The activities of AAB dyes upon S-9 metabolic activation were related to their carcinogenic activities in the rat. The potent carcinogen 3-methoxy-4-aminoazobenzene was a potent mutagen for both tester strains. The moderate or weak carcinogens 4'-methoxy-4-aminoazobenzene and AAB were moderate or weak mutagens for one or both of the tester strains. The noncarcinogens 2-methoxy-4-aminoazobenzene and 2,5-dimethoxy-4-aminoazobenzene were non-mutagenic. In contrast to AAB dyes, N-hydroxy-4-aminoazobenzene dyes showed greater mutagenicity than the mother AAB dyes, without S-9 treatment. 4-Nitroazobenzene dyes and 4-nitrosoazobenzene dyes showed mutagenicity without S-9 treatment, and the activities were related to those of the corresponding N-hydroxy-AAB dyes. All 4-nitroazobenzene dyes were mutagenic in the presence of S-9, suggesting the production of mutagens other than N-hydroxy-AAB dyes by the S-9 treatment. The cytotoxicity of azo dyes to bacteria had no apparent relation to the mutagenic activity of the azo dyes. Incubation of 4-nitroazobenzene dyes with TA100 bacteria yielded N-hydroxy-AAB dyes. The synthesis and properties of new N-hydroxy-AAB dyes, 4-nitroazobenzene dyes and 4-nitrosoazobenzene dyes are described. (Author abstract) (27 Refs)

49. MUTAGEN AND ANTI-MUTAGEN IN GINGER, ZINGIBER OFFICINALE.

Nakamura H, Yamamoto T
Biological Inst., Konan Univ., Kobe 658, Japan
Mutat Res; 103(2):119-126 1982

Rhizome juice of ginger contains compounds that both enhance and suppress the mutagenic action of 2(2-furyl)-3-(5-nitro-2-furyl)acryl amide (AF2) and N-methyl-N'-nitro-N-nitrosoguanidine (NTG) on Escherichia coli B/r (strain Hs30). The clear supernatant of filtered, centrifuged mashed rhizome increased the apparent mutagenic effects of AF2 and NTG as determined by reversions to arginine independence of E coli. Diethyl ether extraction of ginger juice, followed by chromatographic separation and mutagenicity tests, revealed that the factor enhancing mutagenesis by AF2 was (6)-gingerol. The same compound also enhanced NTG mutagenicity, and caused reversions and death of bacteria in a concentration-dependent way. The water-soluble and boundary fractions of an ether/water separation of ginger rhizome juice supp ressed the mutagenesis of (6)-gingerol, which remained in the ether fraction. It is suggested that (6)-gingerol may be activated by specific mutagens only, which explains why antimutagenic agents in the rhizome juice were effective in some experiments and not in others. (10 Refs)

50. ANTIMUTAGENIC ACTIVITY OF BROWNING REACTION PRODUCTS .

Chan RI, Stich HF, Rosin MP, Powrie WD
(c/o Stich) Environmental Carciogenesis Unit, British Columbia Cancer Res. Center, 601 West 10th Ave., Vancouver B.C. V5Z 1L3, Canada
Cancer Lett; 15(1):27-33 1982

Antimutagenic effect was tested by exposing Salmonella typhimurium strain TA1535 in suspension to N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in the presence of products of 2 non-enzymatic browning reactions. The browning reaction products were obtained by heating a lysine-fructose mixture at 121 C for 1 hr and by caramelizing D-sucrose at 180 C for 1.5 hr. Solutions of MNNG were prepared by dissolving the carcinogen directly in phosphate-buffered saline (PBS). The second tested carcinogen, aflatoxin B1 was dissolved directly into dimethyl sulfoxide (DMSO) and then diluted with PBS to a final DMSO concentration of 5%. S typhimurium strain TA98 was used for studies involving aflatoxin B1 and the browning reaction products were added to the precarcinogen and an S9 mixture. The toxic effect of aflatoxin B1 + S9 mixture was abolished in the presence of the browning reaction products. The inhibitory action of non-enzymatic browning product reactions was tested on the direct-acting carcinogen and mutagen MNNG. A dose-dependent reduction in the mutagenic activities of both carcinogens was noted in the pres-

ence of the caramelized sucrose products. The mutagenic activity of both carcinogens was significantly suppressed by the browning reaction products. (22 Refs)

51. IN VITRO EFFECT OF SOME MUTAGENS/ CARCINOGENS ON CULTURED FISH CELLS.

Kocan RM, Landolt ML, Bond J, Benditt EP
Dept. Pathology SM-30, Univ. Washington, Seattle, WA, 98195
Arch Environ Contam Toxicol; 10(6):663-671 1981

Mutagenicity and toxicity of N-methyl-N-nitro-nitrosoguanidine (MNNG) and benzo(a)pyrene (BP) were tested in cell line BF-2 derived from the bluegill sunfish (Lepomis macrochirus). Both MNNG and BP exposure resulted in production of ouabain-resistant mutant colonies. The mutation frequency after exposure to MNNG (direct mutagen) was greater than that after exposure to BP (promutagen). BP at 5 and 20 ug/ml produced dose-dependent decreases in cell number. Incubation of BF-2 cells with BP at greater than 5 ug/ml resulted in formation of intracellular crystals. (20 Refs)

52. BANDING KARYOTYPE ANALYSIS OF ASCITES LINES OF RAT THYMIC LYMPHOMA (MEETING ABSTRACT).

Sofuni T, Hayashi M, Ogiu T, Ishidate M
Division of Mutagenesis, National Institute of Hygienic Sciences, Tokyo, Japan
Proceedings of the Japanese Cancer Association 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Eight transplantable ascites lines of rat thymic lymphoma induced by 1-propyl-1-nitrosourea, were analyzed karyotypically by trypsin G-banding method. All ascites lines examined, were found to have near diploid chromosome number (41-43) in their stemlines, and were characterized by duplication of chromosome segment, resulting from trisomy, reciprocal translocation or tandem duplication, except for one line. In the exceptional line, no significant deviation from normal chromosome banding pattern was recognized by the G-method. (no Refs)

53. ESTABLISHMENT OF CELL LINES DERIVED FROM SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS IN HUMANS AND RATS.

Iizuka T, Ichimura S
Dept. Surgery, Natl. Cancer Center Hosp., 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo 104, Japan
Jpn J Clin Oncol; 11(3):487-493 1981

Two esophageal carcinoma cell lines (TH and TS) were established in DM-160 medium containing 20% fetal bovine serum, and their cytology, chromosomes, and electrophoretic lactate dehydrogenase (LDH) isozyme patterns were studied. Three cell lines (R-1, R-2, R-3) from Donryu rats whose esophageal tumors had been induced by N-amyl-N-methyl-nitrosamine were also established, and subjected to the same studies. The modal chromosome numbers were as follows: TH, 46; TS, 59; R-1, 68; R-2, 41; R-3, 73. The LDH isozyme pattern studied in the TH cell line indicated a tumor pattern. Human tumor cells were sc transplanted to BALB/C nude mice; rat cell lines were transplanted to both mice and Donryu rats. All cell transplants to nude mice resulted in tumors, but transplants in syngeneic Donryu rats did not develop into tumors. (8 Refs)

54. MUTAGENESIS IN FETAL RAT EPIDERMAL CELLS AND EFFECT OF TUMOR PROMOTER, 12-O-TETRADECANOYL-PHORBOL-13-ACETATE (MEETING ABSTRACT).

Indo K, Miyaji H
Department of Pathology, Hyogo College of Medicine, Nishinomiya, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The effect of a tumor promoter, 12-O-tetradecanoyl-phorbol-13-acetate (TPA) on the frequency of mutation from 6-thioguanine (6TG) susceptibility to resistance of the aneuploid fetal rat epidermal cells by chemical carcinogens have been examined. Twenty-four hr treatment of wild type cells by 1 ug/ml dimethylbenzanthracene (DMBA) or 0.1 ug/ml N-methyl-N'-nitro-N'-nitrosoguanidine (MNNG) induced 6TG mutants at the frequency of 49.4 x 10(-6) and 21.2 x 10(-6), respectively. The wild type cells totally died in the medium containing more than 0.1 ug/ml 6TG. However, carcinogen-induced 6TGr mutants showed 70% survival in the medium containing 1 ug/ml 6TG. Yield of 6TGr mutants was enhanced under the continuous existence of 10 ng/ ml TPA after carcinogen treatment. (no Refs)

CELLULAR EFFECTS OF NITROSO COMPOUNDS

55. MULTISTEP ORIGIN OF TUMOR-FORMING ABILITY IN CHINESE HAMSTER EMBRYO FIBROBLAST CELLS.

Smith BL, Sager R
Sidney Farber Cancer Inst., Boston, MA, 02115
Cancer Res; 42(2):389-396 1982

Twenty-one anchorage-independent subclones and 10 subclones with reduced serum requirements were isolated as single-step mutants spontaneously or after ethylmethanesulfonate or N-methyl-N'-nitro-N-nitrosoguanidine mutagenesis of CHEF/18 diploid Chinese hamster embryo fibroblasts. Anchorage-independent mutants retain the high serum requirement and nontransformed morphology typical of CHEF/18. Only four of 21 anchorage mutants have spontaneously produced tumors when injected at 10(7)/site in nude mice, and these were only at a fraction of sites. Low-serum (LS) mutants acquire transformed morphology and increased anchorage-independent growth simultaneously with the loss of high-serum requirement. Only 2 of 10 LS mutants have spontaneously produced tumors. However, when some anchorage and LS mutants were remutagenized and when mutagenized populations were injected into nude mice, tumors appeared at many of the injected sites. In contrast, untreated CHEF/18 cells have never given tumors (0 of 34 sites), and mutagenized CHEF/18 cells have given tumors at only 3 of 29 sites. These results demonstrate that malignant transformation is a multistep process in the Chinese hamster embryo fibroblast system. Most one-step mutants selected for anchorage independence or reduced serum requirements do not have tumor-forming potentials higher than that of the parent CHEF/18. Thus, anchorage-independent and LS phenotypes per se do not account for the increase in tumor-forming potential. It is proposed that the genomic rearrangement process as well as specific mutations may contribute to tumorigenicity. (Author abstract) (67 Refs)

56. CELLULAR DNA DAMAGE BY NITROSOCIMETIDINE: A COMPARISON WITH N-METHYL-N'-NITROSO-NITROSOGUANIDINE AND X-IRRADIATION.

Henderson EE, Basilio M, Davis RM
Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Chem Biol Interact; 38(1):87-98 1981

Permanently proliferating lymphoblastoid cell lines (LCLs) and normal unstimulated peripheral blood leukocytes have been used to study the effects of nitrosocimetidine (NC) on cultured human lymphoid cells. The approaches that were used to assess the cells' ability to cope with NC were: (i) determination of cell survival as measured by colony formation in microtiter plates; (ii) quantitation of DNA synthesis and DNA-repair replication by isopyknic sedimentation of DNA density labeled with 5-bromo-2-deoxyuridine (BrdU); (iii) measurement of the induction of alkali labile lesions and strand breaks by NC in 3H-labeled DNA using velocity sedimentation in alkaline sucrose. In summary, treatment with NC was found to inhibit both replicative DNA synthesis and colony formation in LCLs. At the molecular level, NC treatment induced alkali labile lesions in LCL DNA and elicited DNA-repair replication in proliferating LCLs as well as unstimulated lymphocytes. Considered in total, these data indicate that NC is reactive with human DNA in the cellular environment in a manner similar to methylating nitroso compounds which have been shown to be carcinogenic. The significance of these findings will be discussed. (Author abstract) (25 Refs)

57. LIMITED CAPACITY FOR THE REMOVAL OF O6-METHYLGUANINE AND ITS REGENERATION IN A HUMAN LYMPHOMA LINE.

Sklar R, Brady K, Strauss B
(c/o Strauss) Dept. Microbiology, Univ. Chicago, 920 East 58th St., Chicago, IL, 60637
Carcinogenesis; 2(12):1293-1298 1981

The Raji human lymphoma line is able to remove O6-methylguanine (O6MeG) lesions introduced by treatment of cells with N-methyl-N'-nitro-N-nitroso-guanidine (MNNG). The reaction has a rapid phase in which approx 40% of the O6MeG is removed in the first 10 min. The capacity of cells for rapid O6MeG removal is limited and is saturated at concentrations of MNNG which do not saturate the systems removing 3-methyladenine. Pretreatment of cells with MNNG inhibits their ability to remove O6MeG produced by a subsequent dose given after 2 hr. Treatment with N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) is effective in diminishing cellular capacity for O6MeG removal, and cells unable to remove O6MeG and sensitive to the cytotoxic effects of MNNG are also more sensitive to ENNG than their removal competent counterparts. Regeneration of the ability to remove O6MeG requires incubation of cells for periods greater than 24 hr. The O6MeG removal system is similar to that found in adapted Escherichia coli although the capacity of the Raji lymphoma line is much lower than that of the induced bacteria per unit of DNA. (Author abstract) (35 Refs)

58. ALTERED DNA REPAIR IN FIBROBLASTS FROM AGED RATS.

Fort FL, Cerutti PA
Dept. Toxicology, Abbott Lab., North Chicago, IL, 60064
Gerontology; 27(6):306-312 1981

The role of DNA repair in the aging process was studied using fibroblast cultures derived from rats at the beginning (3 wk) and the end (2 yr) of their potential lifespan. The effect of treatment of the cultures with the DNA-damaging agent, ethylnitrosourea, on the integrity of the pre-existing, parental DNA and on de novo DNA synthesis was determined using the alkaline elution method. It was found that drug treatment resulted in lower levels of fragmentation of parental DNA and in decreased fractions of short daughter strands in cells derived from old relative to young animals. These results indicate an alteration of the processing of DNA damage in cells derived from aged rats. (Author abstract) (37 Refs)

59. EFFECT OF CAFFEINE ON CELL KILLING, MUTATION INDUCTION, DNA REPAIR, AND DNA SYNTHESIS AFTER TREATMENT WITH ETHYL-NITROSOUREA.

Goth-Goldstein R, Painter RB
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Carcinogenesis; 2(12):1267-1271 1981

The effect of caffeine on cell killing, mutation induction, DNA repair, and inhibition of DNA synthesis was investigated in a clonal derivative of M3-1 Chinese hamster cells after treatment with N-ethyl-N-nitrosourea (ENU). Caffeine enhanced cell killing but had no effect on the mutation frequency/ viable cells for the two genetic markers, 6-thioguanine resistance and ouabain resistance. The removal of ethylated purine bases from DNA was as follows: most of the 3-ethyladenine was lost in 20 hr (greater than 85%) and approx 45% of the 7-ethylguanine was lost in 45 hr, whereas 75-93% of the O6-ethylguanine was still present at this time. Caffeine did not seen to influence these rates significantly. The ENU-induced inhibition of DNA synthesis was reversed by caffeine. It is concluded that the potentiation of ENU-induced cell killing by caffeine is caused by the increased frequency of DNA replication past damaged sites in parental DNA. (Author abstract) (25 Refs)

60. EFFECT OF COPPER ADMINISTRATION ON THE INCORPORATION OF [3H]THYMIDINE INTO THE LIVER DNA OF RATS STIMULATED BY DIMETHYLNITROSAMINE AND DIETHYLNITROSAMINE.

Sakai K, Murata N, Chiba K, Yamane Y
Faculty Pharmaceutical Sciences, Chiba Univ., Yayoi 1-33, Chiba 260, Japan
Carcinogenesis; 2(12):1261-1266 1981

The incorporation of [3H]thymidine into liver DNA of rats increased 6-8x 48 hr after a single injection of dimethylnitrosamine (DMN, 30 mg/kg) and diethylnitrosamine (DEN, 100 mg/kg). To test the suppressive effect of copper, the incorporation of [3H]thymidine into liver DNA in the DMN groups or DEN groups pretreated with copper was measured 48 hr after the administration of DMN or DEN. The incorporation of [3H]thymidine into liver DNA of rats stimulated by the injection of DMN was strikingly suppressed by the injection of cupric acetate (20 mg Cu/kg), but that of rats stimulated by the injection of DEN was not suppressed by the injection of copper. Some other metal salts, silver nitrate (20 mg Ag/kg), nickel acetate (20 mg Ni/kg) and basic lead acetate (20 mg Pb/kg) did not significantly suppress the incorporation of [3H]thymidine stimulated by DMN or DEN. The accumulation of copper was much higher in the liver of copper-administered rats than that of nickel or lead in the liver of nickel-administered rats or lead-administered rats. The accumulation of silver was comparatively high in the liver of silver-administered rats. (Author abstract) (27 Refs)

61. HISTOCHEMICAL LOCALIZATION OF CATHEPSIN B AT THE INVASION FRONT OF THE RABBIT V2 CARCINOMA.

Graf M, Baici A, Strauli P
Div. Cancer Res., Inst. Pathology, Univ. Zurich, Zurich, Switzerland
Lab Invest; 45(6):587-596 1981

To clarify the role of cathepsin B in tumor invasion, the enzyme was visualized in tissue frozen sections of the subcutaneously growing rabbit V2 carcinoma. Localization of cathepsin B was achieved by immunofluorescent staining and by enzyme histochemistry. For the former approach, a sheep antiserum was raised against purified cathepsin B from rabbit liver. The antibodies, isolated by immunoadsorption, reacted monospecifically with rabbit liver cathepsin B in Ouchterlony double diffusion and in immunoelectrophoresis. In the enzyme histochemical assay, Z-Ala-Arg-Arg-methoxynaphthylamide was used as fluorogenic substrate and nitrosalicylaldehyde as coupling agent. With both methods, cathepsin B was found to be localized within fibroblasts and leukocytes assembled at the tumor invasion front. In addition, immunofluorescent staining demonstrated the occurrence of the enzyme in the extracellular matrix surrounding tumor cell clusters. Carcinoma cells always remained unstained. The conclusion is drawn that cathepsin B is chiefly produced by host cells which are stimulated to increase synthesis and to release the enzyme under the influence of the tumor. A dual function can be ascribed to cathepin B concentrated in the vicinity of the tumor: it operates intracellularly (in host cells) through degradation of endocytosed protein and extracellularly through activation of collagenase. The resulting lytic action on host structures appears to be a prerequisite for local spread of the V2 carcinoma. (Author abstract) (58 Refs)

62. CHARACTERIZATION OF SPONTANEOUS AND MNNG-TRANSFORMED CELL LINES DERIVED FROM SYRIAN HAMSTER (MEETING ABSTRACT).

Matsuya Y, Kato M, Yamane I
Tohoku University, Sendai, Japan
Proceedings of the Japanese Cancer Association 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Culture of neonatal Syrian hamster lung developed into established cell lines in epidermal growth factor-supplemented medium. The contact-inhibited lines appeared under the condition of low saturation densities and the chromosome number was in tetraploid range. Diploid lines were also isolated from the culture and produced rarely spontaneous transformants during serial culture. The lines became dominant in the population and the chromosome distribution ranged from hypodiploid to hypertetraploid. The cultured line could be transformed by treatment with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and the transformants formed foci showed piling up. The culture was composed of diploid and tetraploid cells. The tumorigenicity of spontaneous and MNNG-transformed cells is now being tested. (no Refs)

63. ESTABLISHMENT OF CHICK FIBROBLASTIC CELL LINE (MEETING ABSTRACT).

Ogura H, Fujiwara T, Namba M, Yabe Y
Department of Virology, Cancer Institute, Okayama University, Okayama, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Primary cultures of chf negative C/O chick embryonic cells were treated with 10 ug/ml of methylnitronitrosoguanidine for 60 min, maintained in minimum essential medium supplemented with 5% calf serum, 1% chick serum, kept in a C0(2) incubator at 41C and transferred periodically. They are now in the 135th passage (18 mo). They form colonies in soft agar but do not produce tumors in chicken. Chromosome analysis revealed the presence of chick-specific chromosomes. They produce avian endogenous virus. (no Refs)

64. THE EFFECT OF NITROSOUREA ANTITUMOR AGENTS UPON THE TRANSGLUTAMINASE ACTIVITY OF MICE LYMPHOMA CELLS (MEETING ABSTRACT).

Szabo T, Fesus L, Laki K
University Medical School, Debrecen, Hungary
Ninth Congress of the Haematological Society, October 1-3, 1981, Debrecen, Hungary. The Society 175 pp., 1981.

The transglutaminase activity of the L1210 leukemia cells of DBA2 mice (in the maintaining form of ascites) and the YPC1 plasmocytoma cells, growing in CAF1, mice was reduced by 40-50% after the subcutaneously administered BCNU or NCNU (1,3-bischloroethyl-1-nitrosourea and 1-chloroethyl-3-neopenthyl-1-nitrosourea) in the usual dose. The in vitro incubation of the cells with the nitrosoureas resulted in a significant inhibition (30%) during 60 minutes. These results support the authors hypothesis about the role of transglutaminase in masking tumor-cells. The increased immunogenity of nitrosourea treated cells, the range of cytotoxic reactions against them also indicate the accuracy of the above hypothesis. To decide, whether the activation, and after nitrosourea administration, the inhibition of the enzyme ensues in vivo, and to search for the direct connection with the immunologic phenomena, a comparison had been done between the free cytoplasmatic and the membrane bound for the nitrosoureas in vivo unavailable-transglutaminase activity. (no Refs)

65. INCREASES IN PROTEIN A24 FOLLOWING TREATMENT OF EHRLICH ASCITES TUMOR CELLS WITH 1-METHYL-1-NITROSOUREA AND 1,3-BIS(2-CHLOROETHYL)-1-NITROSOUREA.

Dornish JM, Smith-Kielland I
Dept. Biochemistry, Univ. Oslo, Blindern, Oslo 3, Norway
FEBS Lett; 136(1):41-44 1981

Following treatment of Ehrlich ascites cells with 1-methyl-1-nitrosourea (MNU) and 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), densitometric analysis of one-dimensional gels revealed that protein A24 (a conjugate of histone H2A a ubiquitin) increased in a dose-dependent manner, while protein synthesis was totally inhibited. Treatment of cells with 50 ug/ml BCNU led to 247x more A24 than in control cells. Treatment with 200 ug/ml MNU led to 307x more A24 than in controls. Increases of protein A24 were also demonstrated by two-dimensional gel electrophoresis. The simultaneous presence of puromycin (20 ug/ml) had no effect of protein A24, indicating that protein synthesis was not responsible for the larger amounts of A24 seen after nitrosourea treatment. Possible ways in which nitrosoureas could cause the apparent increases in protein A24 included alkylation by BCNU and MNU changing the structure of protein A24 and preventing its cleavage mediated by A24 lyase, preventing A24 cleavage through DNA crosslinking, or inhibition of A24 lyase nitrosourea-treated cells. (23 Refs)

IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS

66. LYMPHOCYTES REACTIVITIES AGAINST RAT NEUROGENIC TUMOR: NATURAL KILLER AND SUPPRESSIVE ACTIVITIES.

Tokuriki Y
Dept. Neurosurgery, Kyoto Univ. Medical Sch., Kyoto, Japan
Nippon Geka Hokan; 50(6):809-825 1981

Cell-mediated immune response of lymphocytes from several sources to T1 tumor cells was studied in rats by direct microtoxicity assay. T1 neurinoma was induced by transplacental exposure to ethyl nitrosourea. Syngeneic rats were then inoculated by sc injection of T1 cells. Lymphocytes from spleen, (SL), thymus (TL), lymph node (LNL), and peripheral blood (PBL) of inoculated rats were tested for response to T1 cells. SL exhibited natural killer (NK) activity and suppressive activity (SA). TL and LNL exhibited killer activity (KA). PBL exhibited primarily NK activity, but also some KA. Memory cells activated SA and KA in the presence of tumor antigen. Weak tumor antigen induced SA within 3 days after inoculation and KA within 7 days after inoculation. NK activity and KA were inhibited by SA. Memory cells were neutralized by high levels of antigen associated with advanced tumor growth; SA decreased before KA, indicating that SA was produced by lymphocytes with a shorter life-span than those producing KA. NK activity decreased as tumors reached terminal stages. Strong tumor antigen induced a high level of KA; little or no SA was induced. Inoculation in the brain tissue produced strong KA but no SA. Results suggest that immunotherapy for tumors will require boosting NK activity and KA and control of SA. (41 Refs) (In JPN)

67. ONCORNA VIRUSES IN N-METHYL-N-NITROSOUREA-INDUCED LYMPHOMAS IN MICE.

Pinter A, Borzsonyi M, Torok G, Surjan A, Csik M
Orszagos Kozegeszsegugyi Intezet, Budapest, Hungary
Magy Onkol; 25(4):227-235 1981

Fifteen newborn (C57BL/6xDBA/a) F1 (BDF1) hybrid mice were treated with N-methyl-N-nitrosourea (MNU: 20 mg/kg ip). Five of the 15 animals developed thymic lymphomas, identified histologically and immunologically as lymphoblastic lymphomas, during the 145-day observation period, but no tumors were found in the 20 control animals treated with physiological saline soln only. Unlike the thymic cells of the young control animals, the tumor cells produced oncorna viruses growing in murine tissues only. According to their protein expression, the endogenous, N-tropic viruses represent a homogeneous population. Similar virus was found in thymic cells of a 5-mo-old mouse, which suggests the possibility of age-dependent, spontaneous activation. Since spontaneous lymphoma does not occur in BDF1 mice under the age of 1.5 yr, the viruses isolated are probably not oncogenic, but possess a tumor-promoting property. (19 Refs) (In HUN)

68. TRANSFORMING RNA: CONSIDERATIONS ON THE MECHANISM OF LEUKEMOGENESIS IN MICE (MEETING ABSTRACT).

Hamada K, Yanagihara K, Kajitani T, Kamiya K, Seyma T, Yokoro K
Department of Pathology, Hiroshima University, Hiroshima, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Although the causative implication of a virus in induction of leukemia in mice has long been suspected, a unified concept of leukemogenic mechanism has not been wholly established, due partly to the fact that many mouse strains are naturally infected with C-type RNA retroviruses. Leukemias developed at a high rate in NIH/Swiss mice following administration of N-nitrosoethylurea (NEU). An agent, which transforms cells of several species in vitro and appears to be leukemogenic in collaboration with endogenous MuLV, was isolated from thymi of NEU-induced leukemic mice. The cell transforming capacity of the agent was completely destroyed by treatment with RNase but was not affected by DNase. RNA extracted from SC-1 mouse cells transformed by the agent also showed cell transforming ability. These findings imply that chemical or physical agents exert their leukemogenic activity through the induction of RNA molecules containing transcripts of transforming gene of the cellular origin. (no Refs)

69. ENDOGENOUS MULV INFECTION DOES NOT CONTRIBUTE TO ONSET OF RADIATION- OR CARCINOGEN-INDUCED MURINE THYMOMA.

Mayer A, Dorsch-Hasler K
Dept. Pathology, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Nature; 295(5846):253-255 1982

The contribution of endogenous murine leukemia virus (MuLV) to onset of radiation- or carcinogen-induced murine thymoma was examined. The effect of cellular Fv-1 locus on the development of radiation-induced thymic lymphoma was tested to determine whether this form of induced thymoma also requires active MuLV infection. RF/J and BALB/cJ strains of mice were highly susceptible to radiation induction of thymoma. To measure the effect of Fv-1 more directly, the incidence of radiation-induced thymoma was determined in (BALB/c x RF)F1 x RF backcross mice typed for the alleles carried at the Fv-1 locus. Fv-1n homozyg ous and Fv-1n/Fv-1b heterozygous backcross mice were identified by typing each backcross mouse for its phenotype at the Gpd-1 locus, which is closely linked to the Fv-1 locus. The two subpopulations of the backcross did not differ substantially in radiation-induced thymoma incidences. The finding are not consistent with a requirement for active infection by endogenous MuLV in the development of radiation-induced thymoma. When the backcross mice were typed for their haplotype at H-2, no H-2-associated effect was observed to influence relative resistance to radiation-induced thymoma. RF and 129 mice were chosen for induction of thymoma by N-nitrosomethylurea. Both strains showed high sensitivity. RF mice are much more sensitive to radiation-induced thymoma than 129 mice. F1 hybrid mice also developed a high incidence of the tumor. These findings indicate a basic difference between the etiologies of spontaneous and carcinogen- or radiation-induced thymoma. Spontaneous occurrence of the tumor is associated with expression of endogenous mouse-infectious MuLV activities, including both XC-positive and XC-negative ecotropic MuLV and dualtropic MCF MuLV. Active infection of cells by endogenous MuLV is not essential to development of thymic lymphoma in the mouse following exposure to radiation or chemical carcinogens. (23 Refs)

EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS

70. IN VIVO SKIN PENETRATION STUDIES OF 2,4-TOLUENEDIAMINE, 2,4-DIAMINOANISOLE, 2-NITRO-P-PHENYLENEDIAMINE, P-DIOXANE AND N-NITROSODIETHANOLAMINE IN COSMETICS.

Marzulli FN, Anjo DM, Maibach HI
Natl. Acad. Sciences, Washington, DC
Food Cosmet Toxicol; 19(6):743-747 1981

In vivo skin-penetration capacities of five substances found in cosmetics were studied in humans, monkeys, and swine. Skin penetration of 2,4-toluenediamine was greatest and that of 2,4-diaminoanisole least. Rough estimates of absorbed amounts under normal cosmetic use are given. (21 Refs)

71. NITRITE AND NITROSAMINES IN GASTRIC JUICE: RISK FACTORS FOR GASTRIC CANCER?

Sch[illegible]g P, Bockler R, Peter M
Dept. Surgery, Univ. Ulm, Steinhovelstr. 9, D-7900 Ulm, W. Germany
Scand J Gastroenterol; 17(1):145-150 1982

Nitrite and nitrosamine concentrations have been measured in 108 patients undergoing gastroscopy as a part of routine gastrointestinal investigations. The nitrite and nitrosamine values of 20 patients with duodenal and 11 patients with benign gastric ulcer were within the range of the values of 26 normal subjects. The nitrite and nitrosamine concentrations in 32 patients with inflammatory changes of the gastric mucosa were slightly higher than normal values and correlated with the progressive degrees of the severity. In 19 patients with atrophic gastritis the concentrations of nitrite and nitrosamines were significa ntly elevated in comparison with those of all other groups. Our data suggest a relationship between the constant exposure of an already damaged gastric mucosa to N-nitroso compounds and the known high incidence of gastric cancer in atrophic gastritis. (Author abstract) (11 Refs)

72. NUTRITION AND GASTRIC CANCER.

Joossens JV, Geboers J
33, Capucijnenvoer, B-3000 Leuven, Belgium
Nutr Cancer; 2(4):250-261 1981

Statistical methods and data from different countries were used to study the cause of gastric cancer (GC) and stroke mortality. GC has a multifactorial origin. Possible causes include genetic factors, soil, and nutritional and socioeconomic factors. GC mortality rates are decreasing in 23 of 26 countries studied. Results of multiple regression analysis of the GC-stroke mortality relationship are presented. A strong association was observed for each sex separately and for both sexes combined. Lung cancer is also related to stroke mortality. According to a working hypothesis set forth in 1965, salt intake is the predominant linking factor for both GC and stroke mortality. Thus, stroke would be influenced by the relationship between salt and blood pressure; GC would result from the delaying and caustic properties of stomach hypertonicity, possibly producing atrophic gastritis. Atrophic gastritis favors the synthesis of endogenous nitrites and of nitroso-carcinogens. The salt hypothesis offers an explanation for the geographical and time behavior of GC and stroke mortality, and the socioeconomic gradient of both diseases. GC mortality can also be used to provide a rough estimate of the salt intake in a given country and yr. The influence of salt was tested in Belgium through a deliberate attempt to lower the salt intake of the population. The observed decreases in GC and stroke mortality were consistent with the measured decrease in salt excretion. Monitoring 24-hr salt and creatinine excretion in different countries and over a longer period of time is needed. (72 Refs)

73. CARCINOGENICITY OF CARRAGEENAN.

Hopkins J
British Industrial Biological Res. Assoc.
Food Cosmet Toxicol; 19(6):779-781 1981

The carcinogenic potential of the food stabilizer carrageenan is discussed. Carrageenan has been identified as a cocarcinogen in studies with rats, enhancing methylnitrosourea-, azoxymethane- and dimethylhydrazine-induced colonic carcinoma. Carrageenan may also produce colonic carcinoma when used alone. (no Refs)

74. STUDY OF PRECURSORS OF CARCINOGENIC N-NITROSO COMPOUNDS IN THE SOIL.

Vlasenko NL, Zhuravleva IL, Terenina MB, Golovnia RV, Il'nitskii AP
All-Union Cancer Res. Center, Moscow, USSR
Gig Sanit; (11):15-17 1981

Gas-chromatographic analysis of soil samples showed the presence of primary, secondary, and tertiary aliphatic amines. Since the secondary amines can enter the nitrosation reaction with formation of the carcinogenic nitroso compounds, it was recommended to monitor the soil level of nitrates and nitrites. (16 Refs) (In RUS)

75. ASCORBIC ACID AS A THIOLPRIVE: ABILITY TO INDUCE IMMUNITY AGAINST SOME CANCERS IN MICE.

Knock FE, Gascoyne PR, Sylvester R, Wibel R
Augustana Hosp., 411 West Dickens Ave., Chicago, IL, 60614
Physiol Chem Phys; 13(4):325-333 1981

The potential of ascorbic acid (AA) to act as a thiolprive was investigated by three approaches. Electron spin resonance (ESR) studies showed that administration of AA at a rate of 50 g/60 kg mesothelioma readily generates the ascorbate radical in oxygenated human mesothelioma tissue (spin concentration 6 x 10(15) spins/g dry tissue); thiolprive action was demonstrated by eradication of ESR signal when dithiothreitol was reacted with the tissue. Swiss albino mice infected with ascites cells (Ehrlich and S-180: 10(-2)-10(-4) M) or Ehrlich carcinoma and Sarcoma-180 cells at the same concentration, and treated with AA, exhibited reduced mortality (0/40-12/40) compared with untreated mice (40/40) and with those treated with the agents adriamycin, 5-fluorouracil, methotrexate, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, matulane, vincristine, prednisone, mechlorethamine, thiotepa, and velban (all 40/40). Identically infected mice treated with iodoacetate Synkayvite (Synkayvite is menadiol diphosphate tetrasodium salt) or with iodoacetate alone all survived. Scanning electron micrographs show that S-180 ascites cell surfaces almost entirely lack microvilli after AA treatment at a dosage of 20 g/60 kg cancer tissue, and have no microvilli at all after treatment with AA at a dosage of 2 g/60 kg plus iodoacetate at 480 mg/60 kg. Ascorbate is thought to obtain its antitumor activity, like iodoacetate, through inhibition of sulfhydryl groups. (12 Refs)

☆ U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/119

AUTHOR INDEX WITH CITATION NUMBERS

Aiso S. 21
Akagi M. 38
Andrews AW. 46
Anjo DM. 70
Arai M. 17
Babaya K. 37
Baici A. 61
Basilio M. 56
Benditt EP. 51
Benfield JR. 18
Blackstock SC. 3
Bockler R. 71
Bond J. 51
Borzsonyi M. 67
Brady K. 57
Britt AL. 28
Bryan GT. 38
Burkle V. 31
Caldwell JA. 35
Campbell HA. 9
Campbell RJ. 22
Cerutti PA. 58
Chan FP. 24
Chan RI. 50
Chang CC. 42
Cheung LK. 3
Chiba K. 60
Cohen AH. 18
Colmerauer ME. 39
Csik M. 67
Cui Z. 16
Davis RM. 56
DeLuca C. 25
Degawa M. 48
Dinger N. 35
Domellof L. 36
Dornish JM. 65
Dorsch-Hasler K. 69
Dou G. 16
Duprat J. 7
Emanuel' NM. 8
Enomoto T. 34
Ens B. 24
Epp JK. 43
Fesus L. 64
Flaks A. 19
Flaks B. 19
Fort FL. 58
Frei JV. 24
Fu PC. 18
Fujiwara T. 63
Fukumoto Y. 10
Fukushima M. 39
Fukushima S. 33
Furukawa K. 30
Futatsuki K. 13
Gascoyne PR. 75
Geboers J. 72
Godeneche D. 7
Godin JR. 6
Golovnia RV. 74
Goth-Goldstein. 59
Gotoh H. 34
Graf M. 61
Graupensperger. 41
Guttenplan JB. 45
Hamada K. 68
Hammond WG. 18
Hashimoto Y. 48
Hata S. 34
Hayashi M. 52
Henderson EE. 56
Herren SL. 28
Hill LE. 43
Hirono I. 21
Hirose M. 33
Hopkins J. 73
Hosaka S. 21
Hoshi H. 17
Ichiki H. 14
Ichimura S. 53
Ide G. 29
Iizuka T. 53
Il'nitskii AP. 74
Imbach JL. 2
Indo K. 54
Inoue T. 23
Ishidate M. 52
Ito N. 33
Iversen OH. 32
Izumi T. 14
Jensen T. 18
Johnson RE. 22
Joossens JV. 72
Kajitani T. 68
Kamano T. 14
Kamiya K. 12
Kamiya K. 68
Kanaya H. 1
Katayama S. 27
Kato K. 21
Kato M. 62
Katz M. 47
Kauffman SL. 32
Kazmer S. 47
Khoury MM. 28
Kimura H. 17
Knock FE. 75
Kocan RM. 51
Kodama Y. 12
Koziol JA. 39
Kurihara M. 14
Kusafuka T. 34
Laishes BA. 9
Laki K. 64
Landolt ML. 51
Laws ER. 22
Lee SY. 45
Li Q. 16
Lijinsky W. 20
Lin B. 16
Loo TL. 3
Madelmont JC. 7
Maibach HI. 70
Martinez J. 2
Marzulli FN. 70
Matsuya Y. 62
Mayer A. 69
McCormick DL. 35
McMahon RE. 43
Mehta RG. 35
Minecci LC. 41
Miyaji H. 54
Miyakawa M. 11
Miyamoto S. 34
Miyasaka K. 14
Miyata Y. 37
Mochizuki Y. 30
Montesano R. 26
Monti-Bragadin. 44
Moon RC. 35
Moore MA. 19
Moreau MF. 7
Mori H. 21
Mori H. 36
Mostafa MH. 5
Murata N. 29
Murata N. 60
Muratani M. 17
Nakamura H. 49
Nakamura T. 17
Nakano G. 17
Namba M. 63
Nayak SK. 39
Neal SB. 43
Noda K. 10
Nomura T. 34
Numoto M. 12
Ogiso T. 33
Ogiu T. 52
Ogura H. 63
Ohmori T. 27
Ohtawa M. 29
Oiry J. 2
Okada M. 4
Oki K. 10
Orima H. 14
Oyasu R. 37
Painter RB. 59
Pak HY. 18
Pala M. 44
Paladugu RR. 18
Parodi S. 44
Pereira MA. 28
Peter M. 71
Pienta RJ. 46
Pilch YH. 39
Pinter A. 67
Pitot HC. 9
Plagne R. 7
Poiley JA. 46
Potter VR. 9
Powrie WD. 50
Probst GS. 43
Pulatova MK. 8
Raineri R. 46
Renton KW. 6
Rosin MP. 50

Rubin BA 41
Ruchirawat M 5
Russo P 44
Sager R 55
Sakai K 29
Sakai K 60
Sakamoto K 17
Sakamoto Y 34
Sasajima K 13
Sasaki Y 14
Sawada N 30
Schlag P 71
Schultz RA 42
Schweinsberg F 31
Seyama T 12
Seyma T 68
Sharf VG 8
Shibata K 34
Shirai T 33
Shisa H 13
Shoda K 17
Shors EC 18
Sklar R 57
Smith BL 55
Smith GJ 25
Smith RG 3
Smith-Kielland 65
Sofuni T 52
Stich HF 50
Strauli P 61
Strauss B 57
Sumi Y 11
Sun Y 16
Surjan A 67
Suzuki E 4
Sylvester R 75
Szabo T 64
Takano S 38
Takeda Y 1
Takemoto T 10
Takubo K 13
Tamaro M 44
Taningher M 44
Tasaka K 14
Teplitz RL 18
Terenina MB 74
Thompson CA 35
Thompson CZ 43
Thoms NW 18
Thust R 40
Tokuriki Y 66
Torok G 67
Trosko JE 42
Tsuda H 33
Vaughan K 6
Vlasenko NL 74
Wastell C 15
Watanabe HK 48
Weinstein D 47
Weisburger EK 5
Weisburger JH 36
Wibel R 75
Williams GM 27
Williams GM 36
Winter C 20
Winternitz F 2
Yabe M 17
Yabe Y 63
Yamamoto T 49
Yamane I 62
Yamane Y 29
Yamane Y 60
Yanagihara K 68
Yang DP 41
Yarita T 29
Yasui A 14
Yokoro K 12
Yokoro K 68
Zhang X 16
Zhuravleva IL 74

Keep Up with the Cancer Literature

Each Month
You Can Receive Abstracts
Covering Your Specialty Area

- This convenient service — called Auto SDI* — is as near as your nearest biomedical library. Discuss your research interests with the librarian who will design an appropriate search strategy.
- Abstracts of the latest published literature are searched automatically each month and those related to your interests are delivered to you on a regular basis.
- The abstracts you receive are selected from more than 4,000 monthly entries made into CANCERLIT — the extensive cancer literature data base of the National Cancer Institute.

Talk With Your Librarian
About the Auto SDI Service TODAY.

*Auto SDI stands for Automatic Selective Dissemination of Information. It is a service provided to you, at minimal cost, by the International Cancer Research Data Bank (ICRDB) — a part of the National Cancer Institute.

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. ETHYLENE OXIDE (ETO): EVIDEN CE OF CARCINOGENICITY.
Coene RF
National Inst. for Occupational Safety and Health, Cincinnati, OH
Vet Hum Toxicol; 23(6):439-443 1981

DIETARY FACTORS IN CARCINOGENESIS

2. NUTRITIONAL ASPECTS OF CANCER PREVENTION: AN OVERVIEW.
Silverman J
American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 1 0595
J Am Vet Med Assoc; 179(12):1404-1409 1981

3. FORMATION OF N-NITROSO COMPOUNDS IN FOODS.
Gray JI
Dept. Food Science and Human Nutrition, Michigan State Univ., East Lansing, MI, 48824
ACS Symp Ser; 174():165-180 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

4. LYMPHOMAS AND LEUKAEMIAS. PART 2: TROPICAL AMERICA.
Jimenez E
Hospital Nacional de Ninos 'Dr. Carlos Saenz Herrera', Apartado 1654, San Jose, Costa Rica
Clin Haematol; 10(3):894-915 1981

5. LYMPHOMAS AND LEUKAEMIAS. PART 1: TROPICAL AFRICA.
Olweny CL
Uganda Cancer Inst., P.O. Box 3935, Kampala, Uganda
Clin Haematol; 10(3):873-893 1981

6. MALIGNANT MELANOMA.
Creagan ET
Div. Medical Oncology, Mayo Clinic, Rochester, MN, 55905
Compr Ther; 7(12):36-44 1981

7. MELANOTIC TUMORS OF THE UVEA AND RETINA.
Schmitt H
Universitats-Augenklinik, Theodor-Stern-Kai 7, D-6000 Frankfurt am Main, W. Germany
Med Klin; 76(24):672-675 1981
In GER

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

8. THE NATURAL HISTORY OF CARCINOGENESIS: IMPLICATIONS OF EXPERIMENTAL CARCINOGENESIS IN THE GENESIS OF HUMAN CANCER.
Pitot HC, Goldsworthy T, Moran S
McArdle Lab. for Cancer Res., Dept. Oncology, Medical Sch., Univ. Wisconsin, Madison, WI, 53706
J Supramol Struct Cell Biochem; 17(2):133-146 1981

9. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.
Weinstein IB
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

10. BURKITT'S LYMPHOMA.
Ambrus JL, Ambrus CM
Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Med; 12(6):385-413 1981

11. PRIMARY HEPATIC CARCINOMA.
Ioaquin CJ
Catedra de Medicina Interna A, Facultad de Ciencas Medicas, La Plata, Argentina
Rev Fac Cienc Med La Plata; 4(2):27-31 1981
In SPA

METHODOLOGY IN CARCINOGENESIS RESEARCH

12. MUTAGENESIS AND CARCINOGENESIS TESTING IN VITRO.
Casto BC
Northrop Services, Incorporated, P.O. Box 12313, Research Triangle Park, NC, 27709
Biotechnol Bioeng; 23(12):2659-2671 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER IN THE YEAR 2000. A REVIEW.
Saxen E
Suomen Syoparekisteri, Liisankatu 21 B, 00170 Helsinki 17, Finland
Duodecim; 97(20):1708-1716 1981
In FIN

Compilation of Experimental Cancer Therapy Protocol Summaries

April 1982
Sixth Edition

COMPLIMENTARY COPIES NOW AVAILABLE

CONTENT

This document contains summaries of over 1200 open experimental clinical cancer therapy protocols from countries around the world.

Open protocols are arranged in sections according to the specific type of cancer.

Protocols closed in 1981 are listed by title, number, and investigator in a separate section.

INDEXES

Tumor index
Agent/Modality index
Protocol identification number index

Mail to:
Compilation Request
ICRDB Program
National Cancer Institute
Westwood Building Room 10A18
Bethesda, Maryland 20205

Request for 1982 COMPILATION.
(Print Clearly for use as mailing label)

Name: _____

Address: _____

_____

City/State/Zip: _____

Country: _____

CANCERLINE

More Than Just A Fancy Name

Mention CANCERLINE to your librarian and the world's foremost collection of cancer information is at your disposal. With the help of this computerized data system, you can obtain information on the following:

Cancer Literature

The literature date base, **CANCERLIT**, allows you to survey more than 3,000 biomedical journals for information on your topic of interest. Your search will also alert you to meeting proceedings, monographs, and books published in that area. Informative abstracts averaging 200 words are provided with each citation;

Current Cancer Research

The data base **CANCERPROJ** allows you to retrieve descriptions of current work in any cancer research area. The descriptions, which state research objective, methodology, and experimental results, are supplied for projects underway in 77 countries around the world.

Cancer Therapy Protocols

The **CLINPROT** section of CANCERLINE is designed primarily for clinicians. It provides detailed summaries of currently active experimental protocols for any cancer site, agent, or type.

Ask your biomedical librarian about CANCERLINE.
CANCERLINE is sponsored by the International Cancer Research Data Bank—a program of the National Cancer Institute.

CANCERLINE

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
5285 Port Royal Road
Springfield, Va. 22161

OFFICIAL BUSINESS

Penalty for Private Use, $300

PRINTED MATTER

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF COMMERCE
COM-211

THIRD CLASS
BULK RATE

CK-01

CANCERGRAMS are distributed for the International Cancer Research Data Bank (ICRDB) by the National Technical Information Service (NTIS). **CANCERGRAMS** are available from NTIS on a standing order basis at $2 each for North American Continent addressees and $3 each for other addressees. An NTIS deposit account is required. For a list of subject categories or other information, please write to:

Subscription Section
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161

NOTICE OF MAILING CHANGE

☐ Check here if you wish to discontinue receiving this publication.

☐ Check here if your address has changed and you wish to continue receiving this publication. (Be sure to furnish your complete address including zip code.)

Tear off cover with address label still affixed and send to:

Computer Support Center
ICRDB Program
IIT Research Institute
10 West 35th Street
Chicago IL. 60616

CK 01/82/07

NCI/ICRDB/CK01 82/07

PB82-935107

ICRDB CANCERGRAM

CHEMICAL CARCINOGENESIS

Nitroso Compounds

SERIES CK01 No. 82/07

JULY, 1982

This Cancergram is a service of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM of the U.S. National Cancer Institute. Every few weeks, an updated Cancergram containing abstracts of selected cancer-related articles recently published in more than 3000 journals, and dealing with the topic indicated by the above title, is sent to researchers working in this area. These researchers are identified on the basis of the description of their current research project that has been submitted to the ICRDB Program, directly or via granting agencies.

This Cancergram is prepared by the Cancer Information Dissemination and Analysis Center (CIDAC) for Carcinogenesis Information. ***If this Cancergram is useful and valuable, please send your comments to the CIDAC address below, since future editions depend on user satisfaction and user needs:***

CIDAC FOR CARCINOGENESIS INFORMATION
SCIENCE INFORMATION SERVICES
FRANKLIN INSTITUTE RESEARCH LABORATORIES
20TH AND RACE STREETS
PHILADELPHIA, PA 19103

NEWARK PUBLIC LIBRARY

AUG 16 1982

U. S. GOVT. PUBS.
DEPOSITORY 376

DID YOU KNOW?? EACH CANCERLIT SEARCH THAT PROVIDES YOU WITH USEFUL DATA CAN BE STORED IN THE COMPUTER FOR AUTOMATIC SEARCHING OF NEW DATA EACH MONTH. ASK YOUR LIBRARIAN ABOUT AUTOMATIC SELECTIVE DISSEMINATION OF INFORMATION (AUTO-SDT).

In this issue:

- FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS..... 1-5
- METABOLISM OF NITROSO COMPOUNDS..... 6-8
- INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS..... 9-17
- MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS..... 18-24
- MUTAGENICITY OF NITROSO COMPOUNDS..... 25-34
- CELLULAR EFFECTS OF NITROSO COMPOUNDS..... 35-39
- TRANSPLACENTAL EFFECTS OF NITROSO COMPOUNDS..... 40
- IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS..... 41
- EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS..... 42-46
- REVIEWS INCLUDING NITROSO COMPOUNDS..... 47

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20.3173/2:

FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS

1. ENDOGENOUS FORMATION OF N-NITROSO COMPOUNDS.

Tannenbaum SR, Goldman P, Goldin BR, Moore WE, Magee PN, Montesano R, Eisenbrand G
Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Banbury Rep; 7:269-273 1981

Although there is circumstantial evidence for the endogenous formation of N-nitr oso compounds, the low reported levels of these substances in body fluids and tissues (ppb or less) raise serious questions about artefact formation and data interpretation. Experiments on the metabolism of N-dimethylnitrosamine (NDMA) led to the formulation of models which may or may not be accurate. A model of NDMA formation and clearance assumed a steady state between the two processes; the distribution of NDMA in total body water; first-order clearance from the blood; and approx equal rates of NDMA metabolism in rats and humans. In this model, the rate of NDMA clearance in a 70-kg man (total body water, 40 liters) is 0-0.7 ug/liter/hr, and the rate of NDMA formation is 0-10 ug/kg/day (max, 70 ug/day). The real values are probably between these extremes. Studies on urinary NDMA excretion in rats indicated a log/log relationship between the dose and the excreted quantity over 3 orders of magnitude. This model predicted that a blood concentration measured in ppb would be equivalent to a urinary concentration of parts per 10(11). If endogenous formation of N-nitroso compounds occurs in man, the risk would be at least additive to the risk provided by exogenous exposure. If endogenous formation of N-nitroso compounds does occur, it may be possible to limit that exposure by taking appropriate action. (2 Refs)

2. BLOCKING NITROSAMINE FORMATION USING ASCORBIC ACID AND ALPHA-TOCOPHEROL.

Newmark HL, Mergens WJ, Magee PN, Balis ME, Tannenbaum SR, Fine DH, Goldman P, Keefer LK, Montesano R, Archer MC, Wattenberg LW, Eisenbrand G, Balish E, Lipkin M
Product Development and Applications, Hoffmann-La Roche Inc., Nutley, NJ, 07110
Banbury Rep; 7:285-304 1981

N-nitroso compounds are converted in vivo to the reactive, electrophilic nitrosamines. This conversion to the terminal or proximal carcinogens is generally not easily reversed in vivo, so the most practical method of eliminating carcinogenesis by nitrosamines is to prevent their formation by diverting potential nitrosating agents to non-nitrosating substances by the use of appropriate blocking agents. Ascorbic acid and alpha-tocopherol block the formation of N-nitroso compounds in vivo. Because of their mutually complementary actions in aqueous and lipid media, they should be used together. (56 Refs)

3. ACTIVATED N-NITROSOCARBAMATES FOR REGIOSELECTIVE SYNTHESIS OF N-NITROSOUREAS.

Martinez J, Oiry J, Imbach JL, Winternitz F
Equipe de Recherche Associee au CNRS 195, Ecole Nationale Superieure de Chimie de Montpellier, 34075 Montpellier, France
J Med Chem; 25(2):178-182 1982

A practical and convenient method for synthesizing antitumor compounds, N-alkyl-N-nitrosoureas, regioselectively nitrosated on the nitrogen atom bearing the alkyl group is proposed. N-Alkyl-N-nitrosocarbamates are interesting intermediates in these syntheses and yield, by reaction with amino compounds, the regioselectively nitrosated N-alkyl-N-nitrosoureas. As an interesting example, N,N'-bis[(2-chloroethyl)nitrosocarbamoyl]cystamine, a new attractive oncostatic derivative, has been prepared. The cytotoxic activity of these various compounds were tested on L1210 leukemia. (Author abstract) (23 Refs)

4. ANALYSIS OF NITRATE, NITRITE, AND NITROSAMINES IN HUMAN FECES.

Archer MC, Saul RL, Lee LJ, Bruce WR, Hill MJ, Tannenbaum SR, Montesano R, Magee PN, Fine DH, Mergens WJ, Reddy BS
Ontario Cancer Inst., Toronto, M4X 1K9, Canada
Banbury Rep; 7:321-330 1981

The instantaneous concentrations of nitrate, nitrite, and nitrosamines were measured in human feces and the stability of these compounds during incubations with fecal organisms was evaluated. Of eight fecal samples studied, all contained low levels of nitrite and five contained low levels of nitrate, generally less than about 20 umoles/kg, corresponding to a fecal excretion rate of 0.1 mg/day. No nitrosamines were detected in feces. (8 Refs)

5. DETERMINATION OF TRACE AMOUNTS OF NITRITE BY DERIVATISATION AND GAS CHROMATOGRAPHY.

Funazo K, Kusano K, Tanaka M, Shono T
Dept. Applied Chemistry, Faculty Engineering, Osaka Univ., Yamadaoka, Suita, Osaka 565, Japan
Analyst; 107(1270):82-88 1982

Determination of nitrite, which causes methemoglobinemia in infants and may form carcinogenic nitrosamines under certain conditions, was studied. The method utilizes derivatization gas chromatography, in which trace amounts of nitrite are converted into nitrobenzene. The nitrobenzene is subsequently determined by gas chromatography with an electron-capture detector. As little as 0.5 nanog/ml of nitrite can be detected. (17 Refs)

METABOLISM OF NITROSO COMPOUNDS

6. TISSUE-SPECIFICITY OF N-NITROSODIBUTYLAMINE METABOLISM IN SPRAGUE-DAWLEY RATS.

Brittebo EB, Tjalve H
Dept. Toxicology, Univ. Uppsala, Box 573, S-751 23 Uppsala, Sweden
Chem Biol Interact; 38(2):231-242 1982

The distribution and metabolism of N-[14C]nitrosodibutylamine were studied in Sprague-Dawley rats. The results indicated that in addition to the liver, metabolism of the substance occurred in the nasal mucosa, the lung and the esophagus. Metyrapone and diethyldithiocarbamate reduced the production of 14CO2 from N-[14C]nitrosodibutylamine by all these tissues. There was no indication of metabolic capacity in the urinary bladder or the kidney. The results fit with the assumption that tumors of the urinary tract are induced by metabolites reaching these tissues via the urine. Besides the liver, the esophagus and the lung are target tissues for the carcinogenicity of N-nitrosodibutylamine in Sprague-Dawley rats and in these tissues the local formation of reactive metabolites may play a role in the pathogenesis of N -nitrosodibutylamine-induced lesions. (Author abstract) (21 Refs)

7. MONITORING N-NITROSAMINO ACIDS EXCRETED IN THE URINE AND FECES OF RATS AS AN INDEX FOR ENDOGENOUS NITROSATION.

Ohshima H, Bereziat JC, Bartsch H

Programme Environmental Carcinogens and Host Factors, International Agency Res. on Cancer, 150, cours Albert-Thomas, F-69372 Lyon Cedex 08, France

Carcinogenesis; 3(1):115-120 1982

A simple and sensitive method for the quantitative estimation of endogenous N-nitrosation in rats has been developed. This approach is based on the findings that N-nitrosamino acids (eg, nitrosoproline (NPRO), nitrosohydroxyproline (NHPRO) and nitrososarcosine (NSAR)) when administered orally to rats, are excreted unchanged almost quantitatively (88-96% of the dose) in the urine and feces. After sequential administration of a nitrosatable amino acid and sodium nitrite the nitrosamino acid excreted in the urine and feces was analyzed. The amount of NPRO excreted in the urine of rats was proportional to the dose of proline and to the square of the nitrite dose. Co-administration of ascorbic acid and alpha-tocopherol together with the precursors decreased the urinary NPRO whereas thiocyanate increased the yield. After feeding an amino acid precursor and nitrite, the yield of nitrosamino acids formed in vivo and excreted in the urine increased in the order: NPRO less than NSAR less than NHPRO. The same order was seen when the nitrosation rates of the amino acids in vitro were compared. Thus N-nitrosation in vivo in rats occurs via a similar mechanism as observed in vitro. Monitoring of N-nitrosamino acids excreted in the urine and feces thus appears to provide a valuable index for endogenous N-nitrosation. (Author abstract) (31 Refs)

8. EVIDENCE FOR A CYTOCHROME P-420 CATALYZED MECHANISM OF ACTIVATION OF N-HYDROXY-2-ACETYLAMINOFLUORENE.

Reigh DL, Floyd RA

Dept. Math/Science, Univ. Science and Arts of Oklahoma, Chickasha, OK, 73018

Cancer Biochem Biophys; 5(4):213-217 1981

Cytochromes P-450 and P-420 were solubilized from microsomes from perfused livers of phenobarbital-treated male rats. Electron spin resonance spectroscopy revealed the formation of a nitroxyl radical intermediate in the reaction activating N-hydroxy-2-acetylaminofluorene (N-OH-AAF) in the presence of linoleic acid hydroperoxide. The studies suggest the involvement of the P-450 system in conversion of N-OH-AAF to N-acetoxy-2-acetylaminofluorene and 2-nitrosofluorene, and confirm that the P-420 system, whether naturally occurring in microsomes or induced to form P-420 spin forms, is capable of catalyzing peroxidative type reactions. (18 Refs)

INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS

9. CHRONIC OR ACUTE ADMINISTRATION OF VARIOUS DIALKYLNITROSAMINES ENHANCES THE REMOVAL OF O6-METHYLGUANINE FROM RAT LIVER DNA IN VIVO.

Margison GP

Paterson Lab., Christie Hosp., Holt Radium Inst., Manchester M20 9BX, England

Chem Biol Interact; 38(2):189-201 1982

The effect of pretreatment of rats with various symmetrical dialkylnitrosamines on the repair of O6-methylguanine produced in liver DNA by a low dose of [14C]dimethylnitrosamine (DMN) has been examined. DMN, diethylnitrosamine (DEN), dipropylnitrosamine (DPN) or dibutylnitrosamine (DBN) were administered to rats for 14 consecutive weekdays at a daily dose of 5% of the LD50. Animals were given [14C]DMN 24 hr after the last dose and were killed 6 hr later. DNA was extracted from the liver and analyzed for methylpurine content after mild acid hydrolysis and Sephadex G-10 chromatography. While the amounts of 3-methyladenine and 7-methylguanine were only slightly different from controls, the amounts of O6-methylguanine in the DNA of the dialkylnitrosamine pretreated rats were about 30% of those in control rats, indicating a considerable increase in the capacity to repair this base. Liver ribosomal RNA from control and dialkylnitrosamine pretreated rats contained closely similar amounts of O6-methylguanine suggesting that the induced enzyme system does not act on this base in ribosomal RNA in vivo. Pretreatment with these dialkylnitrosamines also enhanced the repair of O6-methylguanine in liver DNA when they were given as a single dose (50% of the LD50) either 3 or 7 days before the [14C]DMN. In addition, single low doses of DMN or DEN (5% of the LD50) given either 1 or 6 days before [14C]DMN increased O6-methylguanine repair and the magnitude of the effect after DEN was similar to that produced by the other pretreatment schedules. The possible mechanism(s) of the induction of O6-methylguanine repair and its relation to hepatotoxicity, DNA alkylation, carcinogenesis and the adaptive response in Escherichia coli are discussed. (Author abstract) (42 Refs)

10. STRAIN AND SPECIES DIFFERENCES IN THE INDUCTION OF ATPASE-DEFICIENT HEPATIC FOCI BY DIETHYLNITROSAMINE.

Laib RJ, Brockes B, Schwaier A, Bolt HM

Abteilung fur Toxikologie, Pharmakologisches Institut, Universitat Mainz, Obere Zahlbacher Strasse 67, D-6500 Mainz 1, W. Germany

Cancer Lett; 15(2):145-148 1982

Quantitation of nucleoside-5'-triphosphate (ATPase)-deficient foci for determination of hepatocarcinogenicity in species other than the rat was examined. Rats, mice, guinea pigs, and tupaias received 5 mg/kg diethylnitrosamine ip 5 days/wk for 3 wk and were killed 6 and 12 wk after treatment was stopped. No ATPase-deficient hepatocellular foci occurred in either of the mouse strains tested (NMRI and B6C3F1) or in tupias. A few foci were observed in guinea pigs 12 wk after cessation of carcinogen treatment. Both rat strains tested developed significantly greater numbers of foci 6 and 12 after ca rcinogen administration than control rats. Sprague-Dawley rats developed more foci than Wistar rats, and female rats of both strains showed a greater response than males. Quantitation of ATPase-

deficient hepatocellular foci as a determinant of hepatocarcinogenesis is restricted to the rat species. (10 Refs)

11. ENZYMATIC, HEMATOLOGICAL AND HISTOLOGICAL STUDIES DURING CARCINOGENESIS OF THE LARGE INTESTINE IN RATS UNDER THE EFFECT OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE.

Przewlocki T, Chlap Z, Czosnek-Dabros E, Szot W
Zaklad Patofizjologii, Instytut Patologii AM, ul. Grzegorzecka 16, 31-531 Krakow, Poland
Patol Pol; 32(2):199-212 1981

The effects of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG; 0.25% aqueous soln) administered as an enema for 7 wk, on enzymatic, hematological and histological characteristics were studied in 64 female Wistar WAG rats during carcinogenesis. Thirty-six other rats served as untreated controls. MNNG did not cause any significant changes in the hematological parameters before the appearance of tumors, but cystic degeneration of the liver was seen in some animals. Changes in the activities of some plasma enzymes were found during the intensive development of the tumors of the colon. The gamma-glutamyl transpeptidase and aspartate transaminase activities increased, and the cholinesterase activity decreased compared with the controls. Among the hepatic enzymes, aspartate transaminase and activity was increased in rats with hepatic cysts between wk 40-60. The alkaline phosphatase activities in the serum and liver showed no abnormal changes compared with the controls. The intensity of the enzymatic disturbances was correlated with the stage of development of the adenomas and adenocarcinomas of the colon. (43 Refs) (In POL)

12. BIOCHEMICAL CHANGES IN MUCOUS MEMBRANE OF RAT STOMACH IN CARCINOGENESIS INDUCED BY N-METHYL-N-NITRO-N-NITROSOGUANIDINE TREATMENT.

Kalinovskii VP, Seitz IF, Vol'fson NI, Petrov AS
N. N. Petrov Res. Inst Oncology, USSR Ministry Health, Leningrad, USSR
Vopr Onkol; 27(12):51-56 1981

Biochemical changes in the stomach mucous membrane of rats treated with N-methyl-N-nitro-N-nitrosoguanidine (MNNG) were studied. Carcinogenesis was shown to involve considerable changes in gastric mucous membrane, eg disorders in biosynthesis of isoforms of pepsinogen-pepsin. Their level and proteolytic activity are gradually declined. This effect can be reversed at an early stage of treatment and is persistent in advanced tumors of glandular part of rat stomach. (Author abstract) (7 Refs) (In RUS)

13. MAMMARY TUMORS INDUCED BY COMBINED TREATMENT WITH NITROSOUREA AND SEX HORMONES.

Ird EA, Smirnova IO
Center for Oncology Res., USSR Acad. Medical Sciences, Moscow, USSR
Vopr Onkol; 27(12):43-46 1981

Transplacental treatment with sinestrol and testosterone-propionate reduces the incidence of spontaneous benign mammary tumors in rats. Treatment of immature female rats with nitrosoethylurea is followed by an earlier development of mammary fibroadenomas. A combined treatment with testosterone-propionate and nitrosoethylurea increases the incidence of mammary fibroadenoma and decreases its mean latent period. Fibroadenoma induction is accelerated by treating adult rats with nitrosoethylurea alone, while combined treatment induces primary mammary tumors at an earlier stage. The morphology of tumors induced by different schemes of combined treatment remains identical. (Author abstract) (8 Refs) (In RUS)

14. IDENTIFICATION OF HUMAN ACINAR CELL CARCINOMA BY MONOCLONAL ANTIBODY AND IN VITRO DIFFERENTIATION.

Parsa I
Dept. Pathology, State Univ. New York, Downstate Medical Center, Brooklyn, NY, 11203
Cancer Lett; 15(2):115-121 1982

Identification of precursor cells of tumors induced by methylnitrosourea (MNU) in organ culture using monoclonal antibody to acinar cells is described. Nude mice were inoculated sc with carcinomas induced by MNU in organ-cultured human pancreas. Tumor nodules developed after 8 wk and were used to establish cell lines. Both monoclonal antibody to acinar cell surface marker produced by hybridoma and in vitro tumor cell differentiation were used to detect tumors of acinar cell origin. One of 14 tumors studied proved to be of acinar cell origin. Fluorescent microscopy revealed strong surface fluorescence. The intensity of fluorescence was much higher than that in normal acinar cells and varied considerably from cell to cell and also on each cell surface. The acinar origin of the tumor was confirmed by its differentiative features after 7 wk of culture. (12 Refs)

15. REACTIVITY OF TUMOR-INFILTRATING, BLOOD, SPLEEN AND LYMPH NODE LYMPHOCYTES AGAINST SYNGENEIC GLIOMA TARGET CELLS.

Stavrou D, Bilzer T, Anzil AP, Hulten M, Kaldrymidou E
Abt. Funktionelle Pathologie, Universitat Munchen, Institut fur Tierpathologie, D-8000 Munchen 22, W. Germany
Anticancer Res; 1(3):125-133 1981

Pleomorphic gliomas were induced in inbred Fischer rats by administration of N-methyl-N-nitrosourea in drinking water and a permanent cell line (78FR-G-219) was established from the primary tumor. Lymphocyte-mediated reactivity was investigated in glioma-bearing rats. Cytotoxic and inhibiting responses of lymphocytes were compared and related to the tumor growth rate and tumor mass at different time intervals. Discontinuous Percoll density gradients were used to enrich tumor-infiltrating lymphocytes (TIL) and Ficoll-Isopaque flotation was used to enrich blood lymphocytes (PBL), spleen lymphocytes (SL), and lymph node lymphocytes (LNL). The reactivity spectrum of isolated lymphocytes raised against cultured 78FR-G-219 cells was monitored by the lymphocyte microcytotoxicity test and colony inhibition ass ay. A reduction of reactivity of PBL, SL and LNL was observed in tumor-bearing rats. TIL exhibited no natural killer (NK) activity, no cytotoxicity against syngeneic 78FR-G-219 cells and no colony inhibition in mixed lymphocyte/target cell cocultivation. In TIL, NK activity was slightly reduced against target cells of a non-cross-reacting syngeneic astrocytoma cell line, 78FR-G-299. These results demonstrate a specific interaction between T cells and pleomorphic glioma cells. (37 Refs)

16. SUBCHRONIC TOXICITY STUDIES ON PENTACHLORONITROSOBENZENE (PCNO) IN FEMALE RATS.

Renner G, Herforth B, Gokel JM, Goerz G, Luderschmidt C
Dept. Pharmacology, Univ. Munich, Nussbaumstrasse 26, D-8000 Munich 2, W. Germany
Ecotoxicol Environ Saf; 5(3):281-290 1981

Toxicity of pentachloronitrosobenzene (PCNO) in female Sprague-Dawley rats was investigated. Animals were fed a diet containing 0, 10, 50, or 100 ppm PCNO for 18 wk. In a long-term skin test, PCNO was applied to the backs of rats in three groups: 0.02% PCNO in diethyl ether, 0.05% PCNO in n-hexane, and 1% PCNO in corn oil, corresponding to daily PCNO doses of 4, 10, and 200 ug, respectively. No abnormalities of condition or behavior were observed in the rats. A slight increase in ferrihemoglobin was dose-related. Levels of SGOT and SGPT were similar; one SGOT value and three SGPT values differed significantly from those of controls. Urinary porphyrin patterns during the last 24 hr of the experiment were not significantly changed. Only the cytochrome P-450 value of the highest dose group differed significantly from the control value. At the level of 100 ppm, concentrations of hepatic glutathione and oxidized glutathione increased to 1.62 and 3.17x those of controls; no significant differences were noted at lower levels. No neoplastic changes were found in any of the organs examined. The exposed skin over the sacral region appeared normal. (21 Refs)

17. LIPIDS OF THE OLIGODENDROGLIAL FRACTION IN METHYLNITROSOUREA INDUCED ENCEPHALOPATHY.

Wender M, Adamczewska-Goncerzewicz Z, Goncerzewicz A, Pankrac J, Talkowska D
Dept. Neurology, Acad. Medicine, 49 Przybyszewskiego Str., 60-355 Poznan, Poland
Exp Pathol; 20(1):64-67 1981

Lipids in oligodendroglial cells isolated from the cerebral white cortex of rats were studied 2-12 wk after administration of a single dose (60 mg/kg) of methylnitrosourea (MNU). Decreases found in sphingomyelin, phosphatidylserine and phosphoinositides correlated with the lipid spectrum in the myelin fraction of MNU-intoxicated rats. (12 Refs)

MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS

18. PROMOTION BY POLYCHLORINATED BIPHENYLS OF ENZYME-ALTERED FOCI IN RAT LIVER.

Pereira MA, Herren SL, Britt AL, Khoury MM
Health Effects Res. Lab., U.S. Environmental Protection Agency, 26 West St. Clai r St., Cincinnati, OH, 45267
Cancer Lett; 15(2):185-190 1982

The number of gamma-glutamyltranspeptidase (GGTase)-positive foci was examined in livers of partially hepatectomized male Sprague-Dawley rats given an initiating dose of diethylnitrosamine (DENA: 0.3 millimole/kg body wt, po) followed 7, 28, or 49 days later by one to three doses of Aroclor 1254 (500 mg/kg, ip). Rats were killed 21 days after the last dose of Aroclor. Incidence of GGTase-positive foci increased from a mean of 0.70 foci/square cm (cm2) liver in solvent (tricaprylin)-treated, partially-hepatectomized, DENA-initiated controls to 2.28 foci/cm2 in animals given a single dose of Aroclor 1254. Maximum enhancement was obtained after two doses, which resulted in 3.47 foci/cm2. Up to three doses of Aroclor did not increase the incidence of GGTase-positive foci in partially-hepatectomized animals that had not received DENA. Aroclor 1254 appears suitable as an inexpensive promotor in a short-term initiation/promotion assay for chemical carcinogens. (20 Refs)

19. METHAPYRILENE EFFECTS ON INITIATION AND PROMOTION OF GAMMA-GLUTAMYL-TRANSPEPTIDASE POSITIVE FOCI IN RAT LIVER.

Couri D, Wilt SR, Milks MM
Div. Toxicology, Dept. Pharmacology, Coll. Medicine, Ohio State Univ., Columbus, OH, 43210
Res Commun Chem Pathol Pharmacol; 35(1):51-61 1982

The initiating and promoting effects of methapyrilene were evaluated using the hepatic enzyme-altered foci bioassay. Male Sprague-Dawley rats were partially hepatectomized and 24 hr later were administered either methapyrilene or nitrosodiethylamine by oral gavage. Subsequently, the animals were promoted with 500 ppm phenobarbital or 200 ppm methapyrilene in drinking water for 8 wk. Fresh frozen sections of liver were then stained and scored for gamma-glutamyl-transpeptidase (GGT)-positive foci. Methapyrilene, when tested as the nominal initiator at a single dose of 50 mg/kg or at two doses of 130 mg/kg and promoted by phenobarbital, did not induce foci above background levels. However, when substituted for phenobarbital as the promoting agent following nitrosodiethylamine initiation, methapyrilene enhanced enzyme-altered foci formation to an equal or greater extent than did the promoter phenobarbital. These results suggest that the carcinogenic effects of methapyrilene may be related to its ability to enhance hepatic tumorigenesis. (Author abstract) (19 Refs)

20. CORRELATION BETWEEN RETINOID INHIBITION OF N-METHYL-N-NITROSOUREA-INDUCED MAMMARY CARCINOGENESIS AND LEVELS OF RETINOIC ACID BINDING PROTEINS.

Mehta RG, McCormick DL, Cerny WL, Moon RC
Lab. Pathophysiology, Life Science Div., IIT Res. Inst., 10 West 35th St., Chicago, IL, 60616
Carcinogenesis; 3(1):89-91 1982

A correlation was made between the ability of retinoids to suppress N-methyl-N-n itrosourea (MNU)-induced mammary carcinogenesis and the levels of cytosolic retinoic acid binding proteins (cRABP) in the cytosol of MNU-induced mammary tumors. Although retinyl acetate and N-(4-hydroxyphenyl)retinamide were found to be effective inhibitors of mammary carcinogenesis in intact hosts, both retinoids were significantly more active in ovariectomized rats than in intact animals. Quantitative analyses of cRABP in the tumors indicated that mammary cancers arising in animals which were ovariectomized 1 wk after MNU administration contained significantly increased concentrations of cRABP compared to cancers appearing in intact rats. In addition, when animals bearing palpable mammary tumors were ovariectomized, the tumors which continued to grow contained significantly higher levels of cRABP than did tumors which stopped growing or regressed. These data suggest that the selective inhibition of ovarian hormone-independent mammary cancer by retinyl acetate and N-(4-hydroxyphenyl)retinamide may be mediated through an increased level of cRABP in tumor cells of ovariectomized hosts. (Author abstract) (21 Refs)

21. STUDIES ON TUMOR-PREVENTING COMPOUNDS: SYNTHESIS OF DERIVATIVES OF RETINOIC ACID.

Xu S, Guo Z, Yuan Z, Li L, Huang L
Dept. Synthetics, Inst. Materia Medica Chinese, Acad. Medical Sciences, Beijing, People's Republic of China
Yaoxue Xuebao; 16(9):678-686 1981

In a search for tumor-preventing compounds with greater activity and lower toxicity than retinoic acid, 27 derivatives of retinoic acid were synthesized. The derivatives were obtained by treating alcohols or amines with retinyl chloride. Nine of the compounds synthesized were tested for their activities in preventing carcinogenesis by nitrososarcosine in animals. Particularly high activity and low toxicity was found for N-(4-ethoxycarbophenyl) retinamide. (7 Refs) (In CHI)

22. PROLACTIN AND PROLACTIN RECEPTOR INTERACTIONS IN NORMAL AND NEOPLASTIC TISSUE.

Kelly PA, Djiane J, Turcot-Lemay L
Dept. Molecular Endocrinology, Le Centre Hospitalier de l'Universite Laval, Qubec G1V 4G2, Canada
Adv Exp Med Biol; 138:211-229 1982

Regulation of hormone receptors in nitroso-methylurea (NMU)-induced mammary tumors, the interaction of prolactin with prolactin receptors, and the down-regulation of prolactin receptors induced by prolactin both in vivo and in vitro are described. Prolactin receptors in NMU-induced tumors are reduced following ovariectomy of animals with newly formed tumors (2.5 mo after NMU injection) or in those animals with tumors present for longer periods. Prolactin receptors appear to have a relatively rapid turnover, based on the rate of receptor replenishment following removal of cycloheximide. (50 Refs)

23. ROLE OF GUT FLORA IN THE GENOTOXICITY OF DINITROTOLUENE.

Mirsalis JC, Hamm TE, Sherill JM, Butterworth BE
Biochemical Gentics Dept., SRI International, 333 Ravenswood Ave., Menlo Park, CA, 94025
Nature; 295(5847):322-323 1982

Role of intestinal microflora in dinitrotoluene (DNT) genotoxicity was studied using in vivo - in vitro hepatocyte DNA repair assay. A group of germ-free (axenic) and of associated with Charles River Altered Schaedler Flora (CRASF) male Fischer-344 rats were given 100 mg/kg sterile DNT by gavage in sterile corn oil. Rats associated with CRASF showed marked increase in unscheduled DNA synthesis (UDS) in hepatocytes after DNT treatment, whereas axenic rats showed no increase in UDS. Large increase in UDS was induced by dimethylnitrosamine given as positive control to rats, confirming the ability of axenic animals to carry out excision repair of DNA after exposure to cytotoxic agents. The cecal contents of each rat were cultured to confirm its bacterial status; those of the associated animals contained the complete CRASF flora. Several of the non-associated animals were found to be contaminated with one or two bacterial strains. Non-associated rats contaminated with Streptococcus faecalis showed a small increase in UDS after DNT treatment, while non-associated rats contaminated with Clostridium perfringens showed no increase. None of the contaminants were CRASF constituents. The absence of UDS in axenic animals indicates that metabolism of DNT by gut flora is a necessary step in the genotoxicity of DNT and indicates the value of the assay in assessing the carcinogenic potential of nitroaromatic compounds. (16 Refs)

24. CANCER AND BEHAVIOR: CONJUGATED EFFECTS OF METHYL NITROSOUREA (MNU) AND CONDITIONED EMOTIONAL RESPONSE (CER) ON EXECUTION OF A PROGRAM OF VARIABLE INTERVAL (VI) AND ON DEVELOPMENT OF NEOPLASIAS IN RATS.

Florez Beltran H, Ardila R
Facultad de Patologia, Universidad de Santo Tomas, Bogota, Colombia
Rev Latinoam Psicol; 13(3):375-401 1981

Of 12 male Wistar rats trained in a program of variable interval until they reached a stable state, 3 received methylnitrosourea (MNU: in 3 different doses), 6 received conditioned emotional response (CER) and MNU (in three different doses), 1 received saline soln, and 2 received CER and saline soln. Total rate of response was proportional to the dosage of MNU. Rats which received CER before MNU developed only medullary neoplasia (medulloblastoma or spongioblastoma), showed less cellular immunity to tumors and more development of neoplasia. Temporal discrimination of subjects, motivation, effects of CER and MNU and their interaction were analyzed. Location of neoplasia was spinal medulla (5), peripheral nervous system (2), and gastrointestinal mucosa (2). Types of tumors observed were medulloblastoma (2), spongioblastoma (3), neurinoma (2), and intestinal adenocarcinoma (2). (54 Refs) (In SPA)

MUTAGENICITY OF NITROSO COMPOUNDS

25. COMPARATIVE EVALUATION OF DIFFERENT PAIRS OF DNA REPAIR-DEFICIENT AND DNA REPAIR-PROFICIENT BACTERIAL TESTER STRAINS FOR RAPID DETECTION OF CHEMICAL MUTAGENS AND CARCINOGENS.

Suter W, Jaeger I
Preclinical Res. Dept. Toxicology Unit, Sandoz Ltd., Basle, Switzerland
Mutat Res; 97(1):1-18 1982

Carcinogenic and noncarcinogenic compounds, including antibiotics, polycyclic aromatics, aromatic amines, alkyl halides, esters, epoxide carbamates and related compounds, nitroaromatics and heterocyclics, nitroso compounds, hydrazine compounds, azo compounds, and other bioactive agents, were tested for mutagenicity with the agar incorporation test (AT) and the spot test (ST). Two paired (DNA repair proficient/repair deficient) Bacillus subtilis systems, H17/M45 and HLL3g/HJ-15, were used, and the repair-proficient Escherichia coli A1157 strain was paired with the repair-deficient strains JC2921, JC2926, JC5519, and JC5547. Results were compared with reported carcinogenicity and/or Ames test mutagenicity, or in some cases with Ames Salmonella (TA1535, TA1537, TA1538, TA98, TA100) assays reported here for the first time. E coli systems yielded a high number of 'no result' findings as well as many false-positive outcomes. B subtilis systems were generally reliable indicators of carcinogenicity, especially if both AT and ST were used. The bacterial DNA-repair tests agreed more often with the Ames test than with carcinogenicity results. When both pairs of B subtilis strains were combined with the Ames assay, excess false-positives did not appear, whereas the number of false-negative findings with carcinogens was reduced. The slightly increased probability of uncovering a suspected carcinogen does not seem to justify in-

clusion of the extra tests in a battery, except when working with chemicals of classes in which the Ames test is known to be less sensitive. (59 Refs)

26. AN EVALUATION OF TESTS USING DNA REPAIR-DEFICIENT BACTERIA FOR PREDICTING GENOTOXICITY AND CARCINOGENICITY. A REPORT OF THE U. S. EPA'S GENE-TOX PROGRAM.

Leifer Z, Kada T, Mandel M, Zeiger E, Stafford R, Rosenkranz HS
Dept. Microbiology, New York Medical Coll., Valhalla, NY, 10595
Mutat Res; 87(3):211-297 1981

Methods for detection of DNA-damaging agents by repair-deficient bacterial assays are reviewed and recommendations for their improved use are made. Literature through April 1979 was searched and 91/276 papers contained analyses of 611 compounds that had been assayed in one or more of 55 pairs of repair-proficient and repair-deficient strains (38 Escherichia coli, 11 Bacillus subtilis, and 6 Proteus mirabilis). Test results and carcinogenicity data were compared in polA and other E coli, and E coli polA and B subtilis systems. In the E coli polA system, 100/269 compounds tested were positive, 35 negative and 134 gave No Test (NT) by the spot method; 24 of the latter compounds tested were also positive in the liquid assay technique. Among 45 compounds with a NT result, 23 were positive in the liquid assay and 22 were negative. When the E coli polA system was compared with other E coli strains, agreement of results was observed for 10 compounds, while 7 that were positive with polA and some of the other E coli strains were negative with WP2uvrA. A 78% correspondence between E coli polA and B subtilis rec assays was observed. Of 71 carcinogens assayed by the polA system, 44 were positive, 10 negative, and 17 gave NT or doubtful results. Of 56 carcinogens assayed with B subtilis, 21 were positive, 9 negative and 26 were NT or doubtful. One noncarcinogen tested in each assay was positive. Of the seven carcinogens assayed in P mirabilis, six were positive. E coli detected the highest percentage of alkyl epoxides and hydroxylamines; B subtilis rec the highest percentage of nitrosamines and sulfur and nitrogen oxides. Advantages and disadvantages of DNA repair assays in bacteria are listed. (98 Refs)

27. DNA REPAIR STUDIES ON DIALLATE, TRIALLATE AND SULFALLATE IN HUMAN CELL CULTURES.

Benigni R, Dogliotti E, Falcone E, Calcagnile A
Laboratorio di Tossicologia, Istituto Superiore di Sanita, Roma, Italy
Mutat Res; 103(3):385-390 1982

Induced unscheduled DNA synthesis (UDS) was measured in cells of the EUE line of epithelial-like cells by (3H)thymidine autoradiography and (3H)thymidine/(14C)thymidine incorporation ratio determined after scintillation counting. Autoradiography studies showed that the structurally related carbamates diallate, triallate, and sulfallate caused a significant, dose-dependent increase in UDS over the range of 10(-6) -10(-4) M, with dose-dependent inhibition at 10(-3) and 10(-2) M. No such effect was observed in the 3H/14C assay although treatment with N-methyl-N'-nitro-nitrosoguanidine and methylmethane sulfonate increased (3H)thymidine incorporation. The present results extend to human cells the suggested mutagenicity and carcinogenicity of these pesticides, which had been previously demonstrated in fungal and animal systems. (12 Refs)

28. EVIDENCE FOR A FAST REPAIR OF APURINIC SITES INDUCED BY N-NITROSO-DIMETHYLAMINE IN RAT LIVER DNA.

Parodi S, Taningher M, Balbi C, Pala M, Santi L
Istituto di Oncologia, Universita di Genova, Genova, Italy
Ital J Biochem; 30(5):375-387 1981

Evidence for a fast repair of apurinic sites induced by N-nitroso-dimethylamine in rat liver DNA is presented. Determination of the number of single stranded breaks after different incubation periods in alkali showed that most were alkali-labile sites, with a half-life of approx 33 min. (24 Refs)

29. MUTAGENICITY TESTING ON NON-SELECTIVELY CLONED CHINESE HAMSTER OVARY CELLS WITH THE PROTEIN-MAPPING METHOD.

Zeindl E, Sperling K, Klose J
Institute fur Humangenetik, Freie Universitat Berlin, Garystrasse 9, D-1000 Berlin 33, Germany
Mutat Res; 97(1):67-78 1982

Protein mapping by two-dimensional electrophoresis (2DE) was used to study the mutagenicity of methylnitrosourea (MNU: 100 ug/ml) on Chinese hamster ovary cells cloned in nonselective media. Protein patterns were compared with respect to qualitative and quantitative differences between corresponding protein spots. Among 26 protein patterns obtained from the group of test clones, two different new protein spots were found, one each in two different patterns. No such variants were found in patterns of untreated clones. Protein spots showing differences in staining intensity or occurring in more than one but not all patterns (quantitative variants) were found more often in the test group. On average the quantitative variability in patterns of treated cells was 100% greater than in the control group. The cellular concentration of single proteins is considered a possible sensitive parameter for mutagenicity testing. (24 Refs)

30. MUTAGENIC EFFECTS OF COMBINATIONS OF CHEMICAL CARCINOGENS AND ENVIRONMENTAL POLLUTANTS IN MICE AS SHOWN BY THE MICRONUCLEUS TEST.

Watanabe M, Honda S, Hayashi M, Matsuda T
Dept. Community Medicine, Toyama Medical and Pharmaceutical Univ., Toyama, Japan
Mutat Res; 97(1):43-48 1982

Combinations of dimethylnitrosoamine (DMN) or N-methyl-N'-nitro-N'-nitrosoguanidine (MNNG) and CdCl2 or polychlorinated biphenyls (PCB) were force-fed to male ddY mice. The Schmidt method of determining polychromatic erythrocytes (PCEs) in bone marrow cells was used to measure mutagenicity. DMN alone gave a clear dose-dependent response, whereas Cd alone did not; Cd + DMN enhanced the PCE frequency over that for the equivalent concentration of DMN alone. Possible enhancement of MNNG effects by Cd was also observed. PCB alone had almost no effect, and no synergistic or additive effect with DMN or MNNG was seen. Corn oil seemed to inhibit DMN activity. The results suggest that some combinations of carcinogens and environmental pollutants can interact in mutagenic activity. (4 Refs)

31. HOST-MEDIATED MUTAGENESIS FOR DETECTION OF MUTAGENS/CARCINOGENS.

Inui N, Nishi Y

Section Cell Biology and Cytogenetics, Biological Res. Center, Japan Tobacco and Salt Public Corporation, Nakogi 23, Hatano, Kanagawa 257, Japan

Gann Monogr Cancer Res; 27:73-84 1982

An in vivo-in vitro combination assay, host-mediated transplacental mutation assay (HTMA), has been established in which somatic cell mutations can be detected and measured quantitatively. Two genetic markers, 8-azaguanine resistance (8AGr) and 6-thioguanine resistance, were used for detection of forward mutations in fibroblasts of Syrian hamster embryos in pregnant mothers. Mutation frequencies increased linearly with increases in the dose of furylfuramide up to 100 mg/kg body wt of the mothers, when given ip or po; higher mutagenicity was observed following po administration than after ip treatment. Data obtained by HTMA on the effects of coadministration of secondary amines and nitrite, which result in formation of nitrosamines, are presented. Administration of morpholine plus sodium nitrite (500 mg/kg, each) markedly enhanced the mutagenic effect. Coadministration of aminopyrine and sodium nitrite had a more mutagenic effect on hamster embryonic cells than single administration of either compound alone. Thus, N-nitroso compounds produced in the body do cause gene mutations in embryonic tissues and organs. The induction of 8AGr mutations was studied in cultured cells from various organs of embryos of pregnant hamsters treated with benzopyrene (BP), nitrosodimethylamine (DMN), and N-nitrosoethylurea (NMU). Treatment with BP at 200 mg/kg produced more 8AGr mutations in embryonic lung cells than in kidney, liver, or brain cells. DMN (200 mg/kg) produced the highest frequency of 8AGr mutations in the embryo liver cells. After NME administration, there was marked increase in 8AGr mutations in brain cells. Detection of somatic mutations by HMTA is discussed. (45 Refs)

32. DIESEL-EXHAUST-PARTICLE EXTRACT ENHANCEMENT OF CHEMICAL-INDUCED MUTAGENESIS IN CULTURED CHINESE HAMSTER OVARY CELLS: POSSIBLE INTERACTION OF DIESEL EXHAUST WITH ENVIRONMENTAL CARCINOGENS.

Li AP, Royer RE

Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P. O. Box 5890, Albuquerque, NM

Mutat Res; 103(3-6):349-355 1982

Dichloromethane extracts of exhaust particles (EP) filtered from the exhaust of diesel passenger cars of five different manufacturers were tested in combination with known mutagens using the Chinese hamster ovary (CHO) hypoxanthine-guanine phosphorylase assay. N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG: 0.5 ug/ml) and benzo(a)pyrene [B(a)P: 0.5 ug/ml] were administered with and without diesel EP extract (60 ug/ml in dimethyl sulfoxide) to CHO cells grown with and without Aroclor 1254-induced rat-liver S9 activator. Mutagenicity of the EP extract alone was uniformly low, but treatment of CHO cells with mutagen plus EP extract consistently yielded a mutant frequency higher than expected. Without S9 activation, combined treatment of EP + MNNG gave a mutant frequency 1.4-1.9 x higher than expected. With S9 activation the EP + B(a)P treatments resulted in an observed mutation frequency 2.8-3.2 x the expected value. The observed enhancement phenomenon is highly reproducible, and also affects sister-chromatid exchanges and mutation to ouabain resistance. (21 Refs)

33. MUTAGENS IN DIESEL EXHAUST PARTICULATE: IDENTIFICATION AND DIRECT ACTIVITIES OF 6-NITROBENZO(A)PYRENE, 9-NITROANTHRACENE, 1-NITROPYRENE AND 5H-PHENANTHRO(4,5-BCD)PYRAN-5-ONE.

Pitts JN, Lokensgard DM, Harger W, Fisher TS, Mejia V, Schuler JJ, Scorziell GM, Katzenstein YA

Statewide Air Pollution Res. Center, Univ. California, Riverside, CA, 92521

Mutat Res; 103(3-6):241-249 1982

Combined chemical/microbiological analyses of diesel exhaust particulate organic matter (POM) are reported. Levels of three nitroarenes 1-nitropyrene (1NP), 9-nitroanthracene (9NA), and 6-nitrobenzo(a)pyrene (6NBP) were determined. A new type of direct mutagen in combustion-generated POM, 5H-phenanthro(4,5-bcd) pyran-5-one (IPAP) had been also determined. The base + neutral/(bn) fractions of dichloromethane (DCM) extracts of diesel exhaust POM were much more mutagenic than the acid fraction in the Ames test with Salmonella strains TA98 and TA98R, and the latter strain, a nitroreductase-deficient isolate of TA98, showed less response, indicating that direct activity of the bn fraction was due to nitro-substituted compounds. The presence of 1NP, 9NA, 6NBP, and IPAP in the bn fraction was confirmed by capillary gas chromatography/mass spectra analysis and other tests. Highly purified samples of the four compounds were compared using the Ames test with the standard mutagens quercetin, 2-nitrofluorene and benzo(a)pyrene, and the other mutagens (1 or 3)-nitrobenzo(a)pyrene and (3 or 1)-nitrobenzo(a)pyrene. 1NP accounted for 20 and 27% of the direct mutagenic activity exhibited by the total DCM extract and bn fraction, respectively. The compound accounts for about 50% of the 'nitroarene' portion of the direct activity, defined here as the difference between TA98 and TA98R responses, whereas 9NA and 6NBP make negligible contributions to the total activity. The activity of the lactone IPAP is reported here for the first time, and UV, fluorescence, and mass spectra data for the compound are given. (47 Refs)

34. METABOLIC ACTIVATION AND MUTAGENICITY OF CARCINOGENIC N-NITRAMINES IN LIQUID-INCUBATION SYSTEM.

Khudolei VV, Bartsch H, Malaveille C

N. N. Petrov Res. Inst. Oncology, USSR Ministry Health, Leningrad International Agency Res. Center, Lyons, France

Vopr Onkol; 27(12):47-51 1981

The study established the mutagenicity of carcinogenic dimethylnitramine and nitromorpholine in a liquid-incubation system using Salmonella typhimurium TA 100 and TA 1530 as indicator, in the presence of hepatic postmitochondrial supernatant obtained from 1254 aroclor-treated rats, oxygen and NADP+ - generating system. Synthesis of mutagenic metabolites of nitramines was in correlation with the level of N-dimethylase activity. Ascorbic acid and disulfiram efficiently inhibited intramune-induced mutagenesis. Metabolic activation of nitramines involves (a) conversion of nitramines to nitrosoamines due to reduction of a nitro group, (b) hydroxylation by means of multi-function oxidases, and (c) heterolysis resulting in the formation of an end metabolite which is actually responsible for carcinogenicity and mutagenicity. (Author abstract) (17 Refs) (In RUS)

CELLULAR EFFECTS OF NITROSO COMPOUNDS

35. CHEMICAL CARCINOGENS TRANSFORM BHK CELLS BY INDUCING A RECESSIVE MUTATION.

Bouck N, Di Mayorca G
Dept. Microbiology/Immunology, Northwestern Univ., Chicago, IL, 60611
Mol Cell Biol; 2(2):97-105 1982

Mechanisms of transformation (TF) by chemical carcinogens were studied in the baby hamster kidney cell line BHK-21 clone 13. Tumorigenic transformed cell lines were derived from BHK cells by exposure to papovavirus (PV), dimethylnitrosamine (DMN), nitrosomethylurea (NMU), or 4-nitroquinoline-N-oxide (4-NQO) or by spontaneous transformation. NMU or 4-NQO produced TF and mutations to 6-thioguanine-resistance (6-TGR) or ouabain-resistance (OR) in a dose-related fashion. Parallel dose-response curves for TF, 6-TGR, and OR suggested that TF and mutation occurred by similar mechanisms. Two frame-shift mutagens, ICR-170 and ICR-191, had dose-response curves for survival and TF that were identical. Both compounds produced temperature-restriction mutations in inverse proportion to frame-shift mutations. Fusion of transformed cells with isogeneic normal cells showed that TF induced by PV behaved as a genetic dominant, but spontaneous or chemically induced TF behaved as a genetic recessive. These genetic patterns were exhibited soon after fusion and also after establishment of hybrid clones. All hybrids were nearly tetraploid. Hybrids showed segregation of TF; transformed phenotype was reexpressed in most cases in the form characteristic of the original transformed parent. Results indicate that chemical carcinogenesis in BHK cells involves induction of a recessive mutation as part of a multistage process. (58 Refs)

36. THE RESPONSE OF A VARIETY OF HUMAN FIBROBLAST CELL STRAINS TO THE LETHAL EFFECTS OF ALKYLATING AGENTS.

Teo IA, Arlett CF
MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton, Sussex BN1 9QG, England
Carcinogenesis; 3(1):33-37 1982

The sensitivities of 15 human fibroblast cell strains to the lethal effects of alkylation damage produced by N-methyl-N-nitrosourea (MNU) and N-ethyl-N-nitrosourea (ENU) have been investigated. Nine cell strains were also investigated for their sensitivities to N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). Included in our survey are representative strains derived from donors with the repair defective syndromes xeroderma pigmentosum (XP) and ataxia-telangiectasia (A-T), as well as strains derived from patients with Cockayne's syndrome, Bloom's syndrome, Huntington's disease and strains derived from individuals with unclassified syndromes. On the basis of our survival data we report that hypersensitivity to MNU is shown by two A-T strains (AT3BI and AT5BI), an XP strain (XP3BR), and strain 46BR derived from a patient with hypogammaglobulinemia. This sensitivity to methylating agents is also shown by strains 46BR and XP3BR when treated with MNNG, but not for strain AT5BI. Sensitivity to ENU is shown by strain 11961 (derived from a sun-sensitive individual), XP3BR and a single Cockayne's syndrome strain CS697CTO. Of the strains studied only XP3BR was sensitive to both ethylating and methylating agents and only 46BR showed a greater than two-fold increase in sensitivity compared to normal. (Author abstract) (45 Refs)

37. NATURE AND REPAIR OF POTENTIALLY LETHAL INJURIES.

Gotlib VIa, Synzynys BI, Trofimova SF, Noskin LA, Saenko AS, Pelevina II
Inst. Chemical Physics, Moscow, USSR
Radiobiologiia; 21(6):818-828 1981

The nature of potentially lethal injuries (PLI) was studied in cultured LL cells irradiated with gamma rays or treated with methylnitrosourea (MNU). Cells irradiated with 600 rads showed repair of PLI; short-term exposure to nontoxic concentrations of the inhibitor of DNA synthesis enhanced the repair of PLI. Elimination of single-stranded DNA breaks after irradiation with 6,000 rads was more effective in the conditioned medium. The repair of double-stranded DNA breaks induced by MNU was observed only in the complete medium. The absence of repair of double-stranded DNA breaks was correlated with the absence of repair of PLI. (40 Refs) (In RUS)

38. COMPARATIVE STUDIES ON ANTI-TUMOR EFFECTS OF NITROSOUREAS, ACNU AND MCNU, ON EXPERIMENTAL BRAIN TUMORS.

Harada K, Kiya K, Okamoto H, Uozumi T
Dept. Neurosurgery, Hiroshima Univ., Hiroshima 734, Japan
Neurol Med Chir (Tokyo); 21(10):1017-1023 1981

Comparative anti-tumor effects of ACNU (1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2 chloroethyl)-3 nitrosourea) and MCNU were studied on 20-methylcholanthrene-induced C57 black mouse malignant gliomas (MG-cells) and rat glial tumors (C6-cells) in vitro and in vivo. The inhibitory effects of ACNU and MCNU in vitro were dependent on dose and time. The concentration showing inhibitory effect was more than 10 ug/ml. ACNU was slightly more effective than MCNU. ACNU significantly inhibited DNA synthesis at concentrations higher than 10 ug/ml, but had no such effect on RNA and protein syntheses. MCNU also inhibited DNA synthesis similar to but less than that of ACNU. By a single intraperitoneal administration on day 5, an increased life span (ILS) was observed with ACNU (120.3% increase) and with MCNU (100.4%). The optimal dose was 25 mg/kg/day for both drugs. The therapeutic ratio, or optimal dose divided by the dose producing an increased life span of 30% over controls, of ACNU was 4.17 and that of MCNU was 6.67. When 25 mg/kg/ day of ACNU was administered intraperitoneally on day 5, 2 out of 10 mice survived over 60 days. In case of MCNU, 1 out of 10 mice survived. A single administration of ACNU or MCNU was more effective for the increased life span compared with intermittent administration. From these results, it is suggested that the new water soluble nitrosourea, MCNU, can be utilized as a chemotherapeutic agent against brain tumors as in the case of ACNU. (Author abstract) (28 Refs) (In JPN)

39. OCCURRENCE IN VARIOUS MAMMALIAN CELLS AND TISSUES OF CA(2)+-ACTIVATED PROTEASE SPECIFIC FOR THE INTERMEDIATE-SIZED FILAMENT PROTEINS VIMENTIN AND DESMIN.

Traub P, Nelson WJ
Max-Planck-Institut fur Zellbiologie, D-6802 Ladenburg, W. Germany
Eur J Cell Biol; 26(1):61-67 1981

Several mammalian cell lines propagated in suspension and monolayer culture and some normal and cancerous tissues from rat, hamster and cat were screened for the presence of the Ca++-activated protease specific for the intermediate-sized filament protein vimentin. Gel permeation chromatography on

Sephacryl S-300 of postnuclear supernatants, and sucrose density gradient centrifugation of extracts from Triton X-100-resistant residual cell structures revealed the presence of the enzyme in all cells and tissues tested. Its apparent mol wt amounted to 100,000. Except in the cases of a spontaneous rat lung tumor and a rat hepatocellular carcinoma induced by diethylnitrosamine, most of the enzyme was released into the postnuclear supernatant during cell or tissue extraction, indicating that it is of cytoplasmic origin. There was no correlation between the enzyme level and the vimentin content of cells and tissues. Rat and hamster liver as well as cat kidney, in which vimentin has not been detected by polyacrylamide gel electrophoresis, were relatively rich in the Ca++-activated protease. The experimental results point at the widespread, if not general, occurrence of the enzyme in mammalian cells. (Author abstract) (33 Refs)

TRANSPLACENTAL EFFECTS OF NITROSO COMPOUNDS

40. FOCAL CEREBELLAR DYSTROPHY CAUSED BY TRANSPLACENTAL ADMINISTRATION OF METHYLNITROSOUREA.

Jirakulsomchok S, Chronister RB, Yielding KL
Dept. Anatomy, Univ. South Alabama Coll. Medicine, Mobile, AL, 36688
Brain Res Bull; 8(1):45-52 1982

Pregnant female CD-1 mice were treated with methylnitrosourea (MNU: 20 mg/kg, ip) on day 16 of pregnancy. The offspring were weaned 3 wk after birth and sacrificed at 3 or 5 wk of age. All MNU-exposed animals showed a markedly reduced brain wt and size. The brains were topographically normal except for the cerebellum, which showed abnormalities of the anterior lobe including the vermis and hemisphere. The cerebellar abnormalities in the MNU-exposed brains included reduced number of granular cells, changes in normal migration patterns of Purkinje cells or related compensatory changes, and severe distortions in the anterior lobe including the vermis. Although extent of Purkinje cell migration varied, the anterior lobe (including the vermis) was clearly the most vulnerable to MNU-induced damage; in effects MNU resembled x-rays, 5-fluoro-2'-deoxyuridine, and DNA-damaging viruses (panleukopenia virus). The abnormalities may be caused by specific DNA or genomic damage, which may also be present in certain mouse strains characterized by spontaneous cerebellar degeneration. MNU, a short-lived (15 min), direct-acting DNA alkylating agent, seems to be a promising tool for investigating regional developmental abnormalities in the CNS. (26 Refs)

IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS

41. POTENTIAL IDENTIFICATION OF CHEMICAL CARCINOGENS IN A VIRAL TRANSFORMATION SYSTEM.

Wilson WW, Khoobyarian N
(c/o Khoobyarian) Dept. Microbiology and Immunology, Sch. Basic Medical Sciences, Univ. Illinois at Medical Center, P.O. Box 6998, Chicago, IL, 60680
Chem Biol Interact; 38(2):253-259 1982

Chemical carcinogens from several diverse chemical classes ie; aromatic amines, polycyclic hydrocarbons, nitrosamines, hormonal derivatives, metals and direct alkylating agents cause a 6.2-60.5-fold increase in the frequency of murine sarcoma virus (MSV)-induced transformation in a normal rat kidney (NRK) cell system. Exogenous metabolic activation with a rat liver S-9 homogenate is required for expression of this activity by procarcinogens. Non-carcinogenic analogs of these compounds fail to cause significant increases in the transformation frequency either with or without prior metabolic activation. Iododeoxyuridine, a mutagen also does not cause enhancement of transformation. This system may serve as the basis for a rapid and quantifiable means of identifying chemical carcinogens while introducing a new model for the understanding of the interactions between oncornaviruses and chemical carcinogens. (Author abstract) (14 Refs)

EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS

42. ANALYSIS OF HUMAN BIOLOGICAL SPECIMENS FOR NITROSAMINE CONTENTS.

Eisenbrand G, Spiegelhalder B, Preussmann R
Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Heidelberg, W. Germany
Banbury Rep; 7:275-283 1981

The effects of several nitrosation inhibitors on the formation of N-nitroso compounds were studied in urine samples spiked with various nitrogenous compounds. Sodium azide was the inhibitor of choice for the assay of nitrosamines. Sodium hydroxide alkalinization was useful in the detection of volatile nitrosamines. Frozen storage of the sample was required for the assay of nitrosamides. Blood and urine samples were obtained from healthy men, up to 3 hr after the ingestion of beer spiked with N-dimethylnitros amine (NDMA: 1 or 60 ppb). No NDMA was detected in the blood before ingestion; 1-3 hr after ingestion, the blood level was 0.2-0.5 ppb. Urinary NDMA excretion was influenced by a number of unknown variables. No NDMA was detected in the urine after ingestion of the lower dose of NDMA. Assays with a detection limit of about 0.1 ppb were performed in samples of urine, postprandial saliva, gastric juice, and feces, mostly from healthy subjects. The assays were uniformly negative, except for one fecal sample from a healthy child (about 0.5 ppb). These results do not support the view that exposure to endogenous nitrosamines plays an important role in human health, although they do not rule out the possibility that endogenous nitrosamine formation may take place under certain circumstances. (14 Refs)

43. NITROSATION REACTIONS OF STOMACH MUCOSAL TISSUE OF THE HUMAN AND DOG.

Rice S, Ichinotsubo D, Stemmerman G, Hayashi T, Palumbo N, Sylvester S, Nomura A, Mower H, Goldman P, Mower HF, Tannenbaum SR, Goldin BR, Fine DH, Hill MJ, Reddy BS, Hecht SS, Newmark H
Dept. Chemistry, Univ. Hawaii, Honolulu, HI, 96817
Banbury Rep; 7:185-203 1981

Gastric mucosa specimens from patients who had received hydroxyzine-HCl (HZ), diazepam (DP) and cimetidine before gastrectomy, were assayed for mutagens in Salmonella strains TA98, TA100, TA1535, and TA1537. Mutagenic activity was identified in 21/65 specimens. High pressure liquid chromatographic assays identified the mutagens as nitrosated metabolites of HZ and DP. The enzymes required to metabolize these agents were never found simultaneously in the same specimen. The antral mucosa seemed to be unique among human gastrointestinal tissues in its ability to produce nitrosated metabolites of HZ and DP. No metabolites of fenantyl were found in the human tissues. Specimens of gastric antral mucosa from dogs (without prior drug treatment) contained several mutagens, mostly of the TA98 direct-acting type, in about 20% of cases. A similar number of mutagens occurred in the lower colon mucosa. The enzymes of the canine antral mucosa were capable of nitrosating HZ, DP, and fenantyl. No mutagenic metabolites were identified when human or canine antral mucosa was incubated with cimetidine in vitro, or in the antrum of a dog treated with dinitrosocimetidine 24 hr previously, but chemically synthesized nitrosated analogs of cimetidine showed mutagenic activity in all Salmonella strains except TA98. No component of the diet or environment is known to be nitrosated by the enzyme system discovered in the human antral mucosa, but the experiments with canine tissues suggested that some dietary or environmental components probably do interact with the nitrosative metabolism of the gastric or colonic mucosa. (4 Refs)

44. IMPLICATIONS OF DIETARY FIBER BREAKDOWN IN THE HUMAN COLON.

Cummings JH, Stephen AM, Branch WJ
MRC Dunn Clinical Nutrition Centre, Old Addenbrookes Hosp., Cambridge, CB2 IQE, England
Banbury Rep; 7:71-81 1981

Metabolism of fiber in the colon and implications for human carcinogenesis are reviewed. Possible hypotheses for the mechanism of the protective effect can be obtained from examining data on the dominant effects of fiber on colorectal function. Dietary fiber is extensively degraded in the colon, leading to production of short-chain fatty acids (butyrate) which may affect colonic cell function. Fiber breakdown also stimulates microbial growth in the colon, leading to increased bulk of the colonic content, faster transit rate, and rerouting of nitrogen metabolism. Fiber fermentation in the colon diverts nitrogen metabolism from ammonia formation (ammonia is more toxic to normal cells than transformed cells) to bacterial protein synthesis. If endogenous nitrite synthesis occurs in the human colon, it may arise from the oxidation of ammonia. The optimum pH for bacterial nitrification in pure cultures and natural ecosystems is alkaline (7.0-8.5). A metabolic consequence of a high-fiber diet may be reducing the colonic pH to a level unfavorable to nitrite synthesis from ammonia, leading to a reduced formation of N-nitroso compounds. The urinary excretion of protein metabolites other than ammonia declines when wheat fiber is added to the diet, showing another change in the direction of nitrogen metabolism in the colon. Any or all these events may be important in protection from colorectal cancer. (56 Refs)

45. METHODS FOR THE RECOVERY OF ORGANIC CARCINOGENS FROM WATER.

Ehrlich K, Cawley G, Klein E
Gulf South Res. Inst., New Orleans, LA
Methods for the Recovery of Organic Carcinogens from Water. Available from National Technical Information Service, Springfield, VA, as PB81-209694:, 41 pp., 1981.

The organic carcinogens benzo(a)pyrene, dieldrin, and N-acetyl-2-aminofluorene were recovered on XAD-2 macroreticular resin in yields of 90% or more from distilled water or seawater and in yields of 40% or more from lake Pontchartrain water containing a high concentration of organic material. The original solutions contained less than 500 parts per trillion of carcinogen. These results show that XAD-2 provides an efficient means for recovering nonpolar organic carcinogens from dilute solutions. More polar carcinogens such as dimethylnitrosamine were not effectively recovered on XAD-2 columns. Since XAD-2 binding would not be selective for carcinogens, the authors investigated methods which might bind carcinogens selectively from a mixture of organic compounds. We tested the ability of the above carcinogens to bind to nucleic acid using direct binding, equilibrium dialysis, nuclei binding, and binding to DNA-cellulose. Radio-labeled carcinogens were used to quantify the amount bound. Either rat liver nuclei (0.1 mg DNA) or DNA-cellulose (1 mg DNA) bound 18% of the acetylaminofluorene and up to 66% of the dieldrin from solutions containing 150 to 280 nmoles of compound. Up to 30% of the benzo(a)pyrene from solutions containing as much as 320 pmoles was bound. Tenfold or lower recoveries were found when direct-binding methods were used. (Author abstract)

46. MUTAGENS IN EXTRACTS OF GASTROINTESTINAL MUCOSA.

Stemmermann GN, Mower H, Rice S, Ichinotsubo D, Tomiyasu L, Hayashi T, Nomura A, Mandel M
Pathology Dept., Kuakini Medical Center, Honolulu, HI, 96817
Banbury Rep; 7:175-183 1981

Mucosal specimens from 60 resected stomachs (31 from stomach cancer patients) and 25 colons (11 from colon cancer patients) were assayed for the presence of mutagenic compounds in Salmonella typhimurium TA98 and TA100. The specimens for assay were not grossly involved with cancer. Nitrosated TA98 mutagens were identified in 32/60 stomach specimens, mostly from the antrum. Both sex and age seemed to play a role in determining whether the antral tissues contained mutagens. The TA98 mutagens derived from the antral mucosa were generally nitrosated derivatives of diazepam, hydroxyzine, and cimetidine (which had been used in anesthesia), which does not mean that these agents are carcinogenic in the stomach or any other organ. However, their presence in the stomach serves as a model for the in vivo generation of nitrosated mutagenic compounds. The metabolic process can occur in the absence of dietary nitrite, provided that the gastric epithelium is exposed to any one of a wide variety of amide precursors. These observations support the epidemiologic findings of an inverse correlation between stomach cancer and the intake of foods containing substances (eg, ascorbic acid and vitamin E) blocking the nitrosation process. The intestinal specimens yielded a wide variety of TA98 and TA100 mutagens, which were not characterized chemically. Some of these mutagens seemed to favor specific sites in the colon. (6 Refs)

REVIEWS INCLUDING NITROSO COMPOUNDS

47. GASTROINTESTINAL CANCER: ENDOGENOUS FACTORS.

Bruce WR, Correa P, Lipkin M, Tannenbaum SR, Wilkins TD
Ontario Cancer Inst., Toronto, M4X 1K9, Canada
Banbury Rep 7: 468 pp., 1981.

The role of diet in cancer was examined. Sessions on gastrointestinal microbiology (microbiological considerations in experimental studies, effect of diet on human fecal flora, metabolism of xenobiotics by intestinal flora, and intestinal bacterial activity and carcinogenesis), fiber (ecology of gut fermentation in man, dietary fiber breakdown in the human colon role of fat, fiber, and other modifiers of intestinal carcinogenesis in cancer prevention), host response to carcinogens (risk factor profiles for individuals at increased risk for colon cancer, fecal mutagens and colorectal polyps, enzymes of normal, premalignant, and malignant colonic cells, role of cytochrome P-450 in colon response xenobiotics, inhibitors of gastrointestinal neoplasia, colonic activation of carcinogens), mutagens (in extracts of gastrointestinal mucosa, nitrosation in stomach mucosal tissue of humans and dogs, isolation of mutagens produced in the human colon by bacterial action, structural studies and properties of mutagens isolated from human feces, bacterial fluctuation tests of mutagenic activity in human feces, intake, formation, and release of mutagens by man), N-nitroso compounds (endogenous formation of N-nitroso compounds, analysis of human biological specimens for nitrosamines, block nitrosamine formation using ascorbic acid and alpha-tocopherol, distribution and metabolism of nitrate and nitrite in rats, analysis of nitrate, nitrite, and nitrosamines in human feces, metabolism of nitrate), bile acids and other lipids (bile salts as tumor promoters, bile acids in colorectal carcinogenesis, and analysis of feces for benzopyrene after consumption of charcoal-broiled beef) and epidemiology and design of future studies (epidemiologic tests of hypothesis relating diet and cancer, large-scale cohort study of diet and selected digestive system cancers, and possible application of mutagenesis testing to cancer epidemiology). (716 Refs)

☆ U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/121

AUTHOR INDEX WITH CITATION NUMBERS

Adamczewska-Gon 17
Anzil AP 15
Archer MC 2
Archer MC 4
Ardila R 24
Arlett CF 36
Balbi C 28
Balis ME 2
Balish E 2
Bartsch H 34
Bartsch H 7
Benigni R 27
Bereziat JC 7
Bilzer T 15
Bolt HM 10
Bouck N 35
Branch WJ 44
Britt AL 18
Brittebo EB 6
Brockes B 10
Bruce WR 4
Bruce WR 47
Butterworth BE 23
Calcagnile A 27
Cawley G 45
Cerny WL 20
Chlap Z 11
Chronister RB 40
Correa P 47
Couri D 19
Cummings JH 44
Czosnek-Dabros 11
Di Mayorca G 35
Djiane J 22
Dogliotti E 27
Ehrlich K 45
Eisenbrand G 1
Eisenbrand G 2
Eisenbrand G 42
Falcone E 27
Fine DH 2
Fine DH 4
Fine DH 43
Fisher TS 33
Florez Beltran 24
Floyd RA 8
Funazo K 5
Goerz G 16
Gokel JM 16
Goldin BR 1
Goldin BR 43
Goldman P 1
Goldman P 2
Goldman P 43
Goncerzewicz A 17
Gotlib VIa 37
Guo Z 21
Hamm TE 23
Harada K 38
Harger W 33
Hayashi M 30
Hayashi T 43
Hayashi T 46
Hecht SS 43
Herforth B 16
Herren SL 18
Hill MJ 4
Hill MJ 43
Honda S 30
Huang L 21
Hulten M 15
Ichinotsubo D 43
Ichinotsubo D 46
Imbach JL 3
Inui N 31
Ird EA 13
Jaeger I 25
Jirakulsomchok 40
Kada T 26
Kaldrymidou E 15
Kalinovskii VP 12
Katzenstein YA 33
Keefer LK 2
Kelly PA 22
Khoobyarian N 41
Khoury MM 18
Khudolei VV 34
Kiya K 38
Klein E 45
Klose J 29
Kusano K 5
Laib RJ 10
Lee LJ 4
Leifer Z 26
Li AP 32
Li L 21
Lipkin M 2
Lipkin M 47
Lokensgard DM 33
Luderschmidt C 16
Magee PN 1
Magee PN 2
Magee PN 4
Malaveille C 34
Mandel M 26
Mandel M 46
Margison GP 9
Martinez J 3
Matsuda T 30
McCormick DL 20
Mehta RG 20
Mejia V 33
Mergens WJ 2
Mergens WJ 4
Milks MM 19
Mirsalis JC 23
Montesano R 1
Montesano R 2
Montesano R 4
Moon RC 20
Moore WE 1
Mower H 43
Mower H 46
Mower HF 43
Nelson WJ 39
Newmark H 43
Newmark HL 2
Nishi Y 31
Nomura A 43
Nomura A 46
Noskin LA 37
Ohshima H 7
Oiry J 3
Okamoto H 38
Pala M 28
Palumbo N 43
Pankrac J 17
Parodi S 28
Parsa I 14
Pelevina II 37
Pereira MA 18
Petrov AS 12
Pitts JN 33
Preussmann R 42
Przewlocki T 11
Reddy BS 4
Reddy BS 43
Reigh DL 8
Renner G 16
Rice S 43
Rice S 46
Rosenkranz HS 26
Royer RE 32
Saenko AS 37
Santi L 28
Saul RL 4
Schuler JJ 33
Schwaier A 10
Scorziell GM 33
Seitz IF 12
Sherill JM 23
Shono T 5
Smirnova IO 13
Sperling K 29
Spiegelhalder B 42
Stafford R 26
Stavrou D 15
Stemmerman G 43
Stemmermann GN 46
Stephen AM 44
Suter W 25
Sylvester S 43
Synzynys BI 37
Szot W 11
Talkowska D 17
Tanaka M 5
Taningher M 28
Tannenbaum SR 1
Tannenbaum SR 2
Tannenbaum SR 4
Tannenbaum SR 43
Tannenbaum SR 47
Teo IA 36
Tjalve H 6
Tomiyasu L 46
Traub P 39
Trofimova SF 37
Turcot-Lemay L 22

Uozumi T. 38
Vol'fson NI. 12
Watanabe M. 30
Wattenberg LW. 2
Wender M. 17
Wilkins TD. 47
Wilson WW. 41
Wilt SR. 19
Winternitz F. 3
Xu S. 21
Yielding KL. 40
Yuan Z. 21
Zeiger E. 26
Zeindl E. 29

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. AN EVALUATION OF THE GENETIC TOXICITY OF EPICHLORHYDRIN. A REPORT OF AN EXPERT GROUP OF THE INTERNATIONAL COMMISSION FOR PROTECTION AGAINST ENVIRONMENTAL MUTAGENS AND CARCINOGENS.
Sram RJ, Tomatis L, Bridges BA, Clemmesen J
(c/o Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):299-319 1981

2. ETHYLENE DIBROMIDE (EDB). (REVISED).
NIOSH Document Development Branch
Robert A. Taft Lab., National Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
Curr Intell Bull NIOSH (37): 13 pp., 1981.

3. CHEMICAL CARCINOGENESIS AND SMOKING.
Farber E
Dept. Pathology, Univ. Toronto, Banting Inst., 100 College St., Toronto, Ontario M5G 1L5, Canada
Can J Public Health; 72(6):381-385 1981

RADIATION CARCINOGENESIS

4. CELLULAR TRANSFORMATION BY RADIATION: INDUCTION, PROMOTION, AND INHIBITION.
Borek C
Radiological Res. Lab., Cancer Center/Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 16(4):311-336 1981

5. EFFECTS OF IONIZING RADIATION ON THE DEVELOPING EMBRYO AND FETUS: A REVIEW.
Hoffman DA, Felten RP, Cyr WH
Bureau Radiological Health, Rockville, MD
Effects of Ionizing Radiation on the Developing Embryo and Fetus: A Review. Available from National Technical Information Service, Springfield, VA, as PB82-115379:, 160 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

6. BETA-CARBOLINES, PSYCHOACTIVE COMPOUNDS IN THE MAMMALIAN BODY.
Airaksinen MM, Kari I
Dept. Pharmacology, Univ. Kuopio, P.O. Box 138, SF-70101 Kuopio 10, Finland
Med Biol; 59(4):190-211 1981

7. DIET AND CANCER OF THE LARGE BOWEL.
Zaridze DG
Analytical Epidemiology Programme, Div. Epidemiology and Biostatistics, International Agency for Res. on Cancer, 150 Cours Albert Thomas, 69372 Lyon, Cedex 2, France
Nutr Cancer; 2(4):241-249 1981

8. INFLUENCE OF DIET ON MAMMARY CANCER.
Carroll KK
Dept. Biochemistry, Univ. Western Ontario, London, Ontario, N6A 5C1, Canada
Nutr Cancer; 2(4):232-236 1981

9. ARTIFICIAL SWEETENERS IN RELATION TO THE EPIDEMIOLOGY OF BLADDER CANCER.
Howe GR, Burch JD
NCI Canada Epidemiology Unit, Univ. Toronto, Ontario, Canada
Nutr Cancer; 2(4):213-216 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

10. EPIDEMIOLOGY AND THE STUDY OF CANCER.
Woods NF, Woods JS
Dept. Physiological Nursing, Sch. Nursing, Univ. Washington, Seattle, WA
Cancer Nursing. Marino LB, ed. St. Louis, The C. V. Mosby Company, 635 pp., 1981.

11. EPIDEMIOLOGY OF CUTANEOUS MALIGNANT MELANOMA.
Balda BR
Dermatologische Klinik und Poliklinik der Universitat, Frauenlobstr. 9-11, D-8000 Munchen 2, W. Germany
MMW; 123(50):1923-1926 1981
In GER

12. THE SMOKING-INDUCED EPIDEMIC.
Doll R
Green Coll. Oxford, Oxford, England
Can J Public Health; 72(6):372-381 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

13. HEALTH HAZARDS OF ASBESTOS EXPOSURE.
Kaw JL
Industrial Toxicology Res. Centre, Lucknow 226 001, India
J Sci Ind Res; 40(5):342-346 1981

14. OVERVIEW OF FINNISH EPIDEMIOLOGIC STUDIES ON OCCUPATIONAL CANCER.
Tola S
Dept. Epidemiology and Biometry, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 7(Suppl4):133-139 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

15. ALKYLATION OF DNA AND TISSUE SPECIFICITY IN NITROSAMINE CARCINOGENESIS.
Montesano R
International Agency for Res. on Cancer, 150, Cours Albert Thomas, 69372 Lyon Cedex 2, France
J Supramol Struct Cell Biochem; 17(3):259-273 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

16. TRANSFORMATION INDUCED BY HERPES SIMPLEX VIRUS: A POTENTIALLY NOVEL TYPE OF VIRUS-CELL INTERACTION.
Hampar B
Lab. Molecular Virology, NCI, Frederick, MD, 21701
Adv Cancer Res; 35:27-47 1981

17. ONCOGENESIS BY RNA TUMOR VIRUSES.
Koyama T
Dept. Carcinostasis Res., Tokyo Univ. Medical Res. Inst., 4-6-1 Kindai, Minato-ku, Tokyo 108, Japan
Tanpakushitsu Kakusan Koso; 26(14):2121-2129 1981
In JPN

18. POLYOMA T ANTIGENS.
Eckhart W
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
Adv Cancer Res; 35:1-25 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

19. EPIDEMIOLOGICAL ASSESSMENT OF DIETARY INTAKE.
James WP, Bingham SA, Cole TJ
Medical Res. Council's Dunn Clinical Nutrition Center, Adenbrooke's Hosp., Cambridge, England
Nutr Cancer; 2(4):203-212 1981

20. ASSESSMENT OF TECHNOLOGIES FOR DETERMINING CANCER RISKS FROM THE ENVIRONMENT.
Office of Technology Assessment
Office of Technology Assessment, Washington, DC
Assessment of Technologies for Determining Cancer Risks from the Environment. Available from National Technical Information Service, Springfield, VA, as PB81-235400:, 243 pp., 1981.

21. ANTIBODIES SPECIFIC FOR DNA COMPONENTS STRUCTURALLY MODIFIED BY CHEMICAL CARCINOGENS.
Muller R, Rajewsky MF
(c/o Rajewsky) Institut fur Zellbiologie (Tumorforschung), Universitat Essen (GH), Hufelandstrasse 55, Essen 1, W. Germany
J Cancer Res Clin Oncol; 102(2):99-113 1981

22. APPLICATION OF THE MICROBIAL MUTATION TEST IN OCCUPATIONAL HEALTH AND ITS FUTURE PROBLEMS.
Takemura N
Dept. Public Health, Jikei Univ., 25-8, Nishi-Shimbashi 2-chome, Minato-ku, Tokyo, 105, Japan
Sangyo Igaku; 23(4):355-365 1981
In JPN

OTHER REVIEWS IN CARCINOGENESIS

23. ARACHIDONIC ACID TRANSFORMATION AND TUMOR PRODUCTION.
Levine L
Dept. Biochemistry, Brandeis Univ., Waltham, MA, 02254
Adv Cancer Res; 35:49-79 1981

24. POLYAMINES IN MAMMALIAN TUMORS PART 1.
Scalabrino G, Ferioli ME
Inst. General Pathology, Univ. Milan, 20133 Milan, Italy
Adv Cancer Res; 35:151-268 1981

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
5285 Port Royal Road
Springfield, Va. 22161

OFFICIAL BUSINESS

Penalty for Private Use, $300

PRINTED MATTER

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF COMMERCE
COM-211

THIRD CLASS
BULK RATE

U.S.MAIL

CK-01

CANCERGRAMS are distributed for the International Cancer Research Data Bank (ICRDB) by the National Technical Information Service (NTIS). CANCERGRAMS are available from NTIS on a standing order basis at $2 each for North American Continent addressees and $3 each for other addressees. An NTIS deposit account is required. For a list of subject categories or other information, please write to:

Subscription Section
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161

NOTICE OF MAILING CHANGE

☐ Check here if you wish to discontinue receiving this publication.

☐ Check here if your address has changed and you wish to continue receiving this publication. (Be sure to furnish your complete address including zip code.)

Tear off cover with address label still affixed and send to:

Computer Support Center
ICRDB Program
IIT Research Institute
10 West 35th Street
Chicago IL. 60616

CK01/82/08

NCI/ICRDB/CK01 82/08

PB82-935108

ICRDB CANCERGRAM

CHEMICAL CARCINOGENESIS

Nitroso Compounds

SERIES CK01 No. 82/08

AUGUST, 1982

This Cancergram is a service of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM of the U.S. National Cancer Institute. Every few weeks, an updated Cancergram containing abstracts of selected cancer-related articles recently published in more than 3000 journals, and dealing with the topic indicated by the above title, is sent to researchers working in this area. These researchers are identified on the basis of the description of their current research project that has been submitted to the ICRDB Program, directly or via granting agencies.

This Cancergram is prepared by the Cancer Information Dissemination and Analysis Center (CIDAC) for Carcinogenesis Information. ***If this Cancergram is useful and valuable, please send your comments to the CIDAC address below, since future editions depend on user satisfaction and user needs.***

CIDAC FOR CARCINOGENESIS INFORMATION
SCIENCE INFORMATION SERVICES
FRANKLIN INSTITUTE RESEARCH LABORATORIES
20TH AND RACE STREETS
PHILADELPHIA, PA 19103

NEWARK PUBLIC LIBRARY

SEP 17 1982

U. S. GOVT. PUBS.
DEPOSITORY 376

VISIT THE ICRDB EXHIBIT AT THE INTERNATIONAL CANCER CONGRESS IN SEATTLE, SEPTEMBER 8-15: MEET THE ICRDB STAFF, FIND OUT WHAT'S NEW, AND GET A FREE CANCERLINE SEARCH ON THE SPOT.

In this issue:

- METABOLISM OF NITROSO COMPOUNDS 1-2
- INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS 3-20
- MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS 21-22
- MUTAGENICITY OF NITROSO COMPOUNDS 23-34
- CELLULAR EFFECTS OF NITROSO COMPOUNDS 35-48
- TRANSPLACENTAL EFFECTS OF NITROSO COMPOUNDS 49-50
- EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS 51-61
- REVIEWS INCLUDING NITROSO COMPOUNDS 62-64

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE20.3173/2:

METABOLISM OF NITROSO COMPOUNDS

1. METABOLISM OF N-NITROSAMINES BY CULTURED HUMAN AND RAT ESOPHAGUS.

Autrup H, Stoner GD
NCI, NIH, Building 37, Room 2C13, Bethesda, MD, 20205
Cancer Res; 42(4):1307-1311 1982

The metabolism of several N-nitrosamines (N-nitrosodimethylamine, N-nitrosoethylmethylamine, N-nitrosodiethylamine, N-nitrosobenzylmethylamine, and N-nitrosopyrrolidine) in cultured human and rat esophagus has been investigated by measuring CO2, metabolites with an oxo group and metabolites bound to DNA. Both acyclic and cyclic N-nitrosoamines were metabolized by rat esophagus. The h ighest level of metabolite binding was seen with N-nitrosobenzylmethylamine, an organotropic carcinogen for the rat esophagus. The binding level was about 100-fold higher than in human esophagus. This compound methylated rat esophageal DNA at positions 7 and O6 of guanine. The level of benzylation in rat was one-tenth the level of methylation. Formation of benzaldehyde exceeded that of formaldehyde plus CO2 by a factor of 6, indicating that the methyl group was preferentially oxidized. N-Nitrosoethylmethylamine was preferentially oxidized by rat esophagus in the ethyl group. The highest binding level to DNA from this compound was observed with the methyl group. No binding was detected to human esophagus. N-Nitrosopyrolidine was oxidized by both rat and human esophagus in the alpha position, as measured by the formation of 2,4-dinitrophenylhydrazone derivative of 4-hydroxybutanal. Binding of metabolites of N-nitrosopyrrolidine to DNA was detected only in rat esophagus. As measured by the formation of both CO2 and formaldehyde, N-nitrosodimethylamine was metabolized by both human and rat esophagus. While most of the radioactivity associated with DNA was found to be incorporated into guanine and adenine, methylation of the guanine positions 7 and O6 was detected by chromatography of the hydrolyzed rat DNA. The results indicate significant quantitative and perhaps qualitative differences between cultured rat and human esophagus in their ability to activate N-nitrosamines, although unknown physiological differences after culture may contribute to this difference. (44 Refs)

2. FORMATION AND IDENTIFICATION OF GLUTATHIONE CONJUGATES FROM 2-NITROSOFLUORENE AND N-HYDROXY-2-AMINOFLUORENE.

Mulder GJ, Unruh LE, Evans FE, Ketterer B, Kadlubar FF
(c/o Kadlubar) Natl. Center Toxicological Res., Dept. Health and Human Services, Jefferson, AR, 72079
Chem Biol Interact; 39(1):111-127 1982

The compounds 2-nitrosofluorene (NOF) and N-hydroxy-2-aminofluorene (N-HO-AF) are potent direct-acting mutagens, derived from metabolic activation of the carcinogen, N-acetyl-2-aminofluorene (AAF). To assess the ability of cellular glutathione (GSH) to detoxify these electrophilic derivatives, we examined the reaction of NOF and N-HO-AF with GSH in vitro. Two reaction products were isolated and identified as glutathionyl derivatives of 2-amino-fluorene (AF) containing an N-S linkage. Amino acid analysis, infrared and NMR (500 MHz) spectroscopy, fast atom bombardment mass spectrometry and analysis of reaction characteristics and hydrolysis products established their structures as N-(glutathion-S-yl)-2-aminofluorene S-oxide (GS-AF1) and N-(glutathion-S-yl)-2-aminofluorene (GS-AFII). Ascorbic acid, which reduces NOF to N-HO-AF, was used to modify reaction yields. These results indicated that GS-AF1 was derived from reaction with NOF and that GS-AFII could be formed from both NOF and N-HO-AF. A reaction scheme is proposed in which NOF reacts with GSH to form an intermediate addition product that can rearrange either to GS-AF1 or be reduced to GS-AFII. The latter could also be formed by direct reaction with N-HO-AF. (Author abstract) (50 Refs)

INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS

3. COMPARATIVE STUDIES OF NEOPLASTIC RESPONSE TO A SINGLE DOSE OF NITROSO COMPOUNDS. 7. THE EFFECT OF N-NITROSOBIS (2-HYDROXYPROPYL)AMINE IN SYRIAN GOLDEN HAMSTERS.

Pour PM, Salmasi SZ
Preclinical Res., Toxicology Dept., Sandoz AG, CH-4133 Pratteln 4, Switzerland
J Cancer Res Clin Oncol; 102(3):265-269 1982

Single sc applications of N-nitrosobis(2-hydroxypropyl)amine (BHP) caused carcinogenic effects in adult Syrian golden hamsters at doses as low as 1/40 of the LD50. The tumor spectrum decreased at lower doses, which affected the pancreas more strongly than the liver, whereas higher doses exhibited a more pronounced hepatocarcinogenicity and also induced tumors in the respiratory tract, gallbladder, kidney, and vagina. These results demonstrated a potent pancreatic carcinogenic effect of BHP at the lowest dose level. Hence, the presence of BHP in the environment, even in small quantities, should be regarded as a potential hazard to human health. (Author abstract) (9 Refs)

4. CARCINOGENICITY OF VINYLETHYLNITROSAMINE IN SYRIAN GOLDEN HAMSTERS.

Green U, Althoff J
Dept. Experimental Pathology, Univ. Medical Sch. Hannover, Karl-Wiechert-Allee 9, D-3000 Hannover 61, W. Germany
J Cancer Res Clin Oncol; 102(3):227-233 1982

Syrian golden hamsters received weekly sc doses of 5.0, 2.5, 1.25 or 0.63 mg/kg bw vinylethylnitrosamine (VEN). As dose levels increased, av survival time decreased, tumor multiplicity increased as did the total tumor rate which was between 50% and 100%. The main target of VEN effect was the respiratory tract where a positive dose-response relationship was established for neoplastic growth. (Author abstract) (18 Refs)

5. CARCINOGENICITIES OF 1-ETHYL- AND 1-AMYL-1-NITROSOURETHANS IN FEMALE DONRYU RATS: DOSE-EFFECT RELATIONS.

Onodera H, Furuta K, Matsuoka C, Kamiya S, Maekawa A
(c/o Maekawa) Div. Pathology, Biological Safety Res. Center, Kamiyooga 1-18-1, Setagaya-ku, Tokyo 158, Japan
Gan; 73(1):48-54 1982

Groups of female Donryu rats were given solutions of 100, 50, and 25 ppm of 1-ethyl-1-nitrosourethan (ENUR), and of 400, 200, and 100 ppm of 1-amyl-1-nitrosourethan (ANUR) continuously in the drinking water. The incidence of tumors was nearly 100% in all groups treated with ENUR or ANUR,

but with both chemicals that rats showed dose-dependent mean survival times. In the groups treated with ENUR, tumors were most frequent in the upper digestive tract and duodenum, whereas in groups given ANUR tumors were induced only in the upper digestive tract, with none in the duodenum. Tumors of the forestomach were more frequent than those of the esophagus and oral cavity and/or pharynx in groups treated with ENUR. In contrast, the target organs of ANUR were the oral cavity and/or pharynx, and the esophagus, rather than the forestomach. The carcinogenicities of these two chemicals are discussed in comparison with those of other 1-alkyl-nitrosourethans. (Author abstract) (16 Refs)

6. THE CARCINOGENIC EFFECT OF 1,1-DIETHYL-3-METHYL-3-NITROSOUREA IN EUROPEAN HAMSTERS.

Ketkar MB, Althoff J, Lijinsky W

Abteilung fur experimentelle Pathologie, Medizinishe Hochschule Hannover, Karl-Wiechert-Allee 9, D - 3000 Hannover 61, W. Germany

Exp Pathol; 20(3):153-155 1981

Laboratory-bred European hamsters received subcutaneous injections of 1,1-diethyl-3-methyl-3-nitrosourea once weekly for life. The animals developed mainly squamous cell carcinomas of the nasal and oral cavities and malignant sarcomas (schwannomas) of the glandular stomach. The av tumor latency was shorter in females (24 wk) than in males (28 wk), while tumor incidence was 80% for both sexes. (Author abstract) (10 Refs)

7. EFFECT OF PHENOBARBITAL ON THE DEVELOPMENT OF TUMORS IN MICE TREATED NEONATALLY WITH N-ETHYL-N-NITROSOUREA.

Naito M, Naito Y, Ito A

Dept. Cancer Res., Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi 1-2-3,, Minami-ku, Hiroshima 734, Japan

Gan; 73(1):111-114 1982

This study was undertaken to evaluate the effect of phenobarbital on the development of neurogenic tumors induced in mice by neonatal administration of N-ethyl-N-nitrosourea (ENU). A total of 185 A/He mice was divided into four groups. Continuous oral administration of phenobarbital (0.05%) in drinking water was commenced 4 wk after birth in Group I. A single injection of 40 mg/kg of ENU was given subcutaneously on the back within 24 hr after birth in Group II. After neonatal injection of ENU, phenobarbital was commenced 4 wk after birth in Group III. Group IV was the untreated control. The experiment was terminated 12 mo after birth. The serum level of phenobarbital at the end of the experiment was 8.7 ug/ml in Group I and 7.0 ug/ml in Group III. Neurogenic tumors were induced only in groups treated with ENU. The incidence was 5.7% in Group II and 10.9% in Group III, though the difference between the two groups was not statistically significant. A total of three tumors (3.0%) was induced in the central nervous system and five tumors (5.1%) in the peripheral nervous system. Histologically, the former were oligodendroglioma and the latter were schwannoma. Lung tumors, lymphomas and hepatic tumors were also induced by ENU, and in male mice phenobarbital had a suppressing effect on the development of liver tumors. (Author abstract) (19 Ref s)

8. THE PRINCIPAL FIELDS OF RESEARCH INTO THE PATHOGENESIS OF GLIOMAS.

Cohadon F

Laboratoire de Neurochirurgie Experimentale et Neurobiologie, Groupe Hospitalier Pellegrin, place Amelie-Raba-Leon, F 33000 Bordeaux, France

Neurochirurgie; 27(5):241-245 1981

Experimental models studying the pathogenesis of gliomas are focused on chemically or viral induced tumors in animals. The transplacental injection of ethyl-nitrosourea in rats has produced a high rate (80-100%) of cerebral tumors of mixed types in the offspring. Repeated injections of methyl-nitrosourea in the adult rat has produced more homogenous cerebral tumors (glioblastomas most often) in 60-70% of the rats. Viral induced tumors have been produced in dogs inoculated at birth with intracerebral injections of Rous sarcoma virus. Glioma promotion is considered a result of the failure of a hypothetical immune mechanism of surveillance. The absence of systemic metastases of the gliomas is an indirect but convincing proof in favor of a surveillance immune system which eliminates the malignant cells when they leave the immunological protection of the brain. This theory is further supported by the clear immunosuppression of some patients with gliomas. At the present time, there is not definite identification of initiation or promotion factors in the pathogenesis of human gliomas. (7 Refs) (In FRE)

9. HORMONAL INDUCTION OF CASEIN GENE EXPRESSION LIMITED TO A SMALL SUBPOPULATION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMOR CELLS.

Supowit SC, Rosen JM

(c/o Rosen) Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030

Cancer Res; 42(4):1355-1360 1982

In the hormonally responsive 7,12-dimethylbenz(a)anthracene (DMBA)- or N-nitrosomethylurea (NMU)-induced mammary carcinomas, regulatory mechanisms have been altered such that these tumors retain their hormonal dependence for growth but possess only a limited ability to synthesize the mammary gland-specific milk proteins. Quantitation of casein mRNA levels revealed that very low levels of casein messenger RNA (mRNA) were expressed in both the DMBA- and NMU-induced tumors growing in virgin animals (0.1 to 0.4% of the maximally induced 8-day-lactating mammary gland). Growth of DMBA-induced tumors in pregnant rats and the treatment of NMU-induced tumor-bearing animals with thioproperazine indicated that the tumor casein mRNA levels were hormone inducible (3.4-and 2.1-fold for the DMBA- and NMU-induced tumors, respectively). However, casein mRNA levels were still only 1 to 2% of those found in the normal mammary gland under the same hormonal environment. Localization of the casein-synthesizing cells in the DMBA-induced tumors by peroxidase-antiperoxidase staining and a specific casein antiserum indicated that, in both control and hormone-treated tumors, the vast majority of cells (greater than 95%) were unabl e to synthesize casein. The hormonal induction of casein mRNA sequences could be correlated with an increase in the number of cells synthesizing casein, which appeared as small clusters of cells throughout the tumors. Therefore, the loss of hormone-regulated differentiated function in these tumors, which maintained hormone-dependent growth, suggests the presence of a defective regulatory mechanism beyond the level of the hormone-receptor complex. (Author abstract) (29 Refs)

10. POLY(ADP-RIBOSYLATION) IN N,N-DIETHYLNITROSAMINE-TREATED MICE.

Shugart L, Chastain B, Holland JM
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Int J Biochem; 14(3):231-233 1982

C3H mice were treated with single injections of N,N-diethylnitrosamine (DEN: 35-100 mg/kg body wt, ip). Liver nuclei of the treated animals were examined for poly(ADP-ribose) and the conjugate enzyme poly(ADP-ribose) polymerase. The poly(ADP-ribose) content increased with time, showing a peak at about 4 hr post-injection and subsequently falling to pre-injection levels. This effect was dose dependent and was not observed in a control experiment which examined the nuclei of the kidney, a non-target tissue of DEN. The level of poly(ADP-ribose) polymerase also exhibited a transitory increase which was dose dependent. The return of poly(ADP-ribose) levels to the pre-injection level is probably not due to the accompanying loss of polymerase activity but instead to the transient induction of poly(ADP-ribose) glycohydrolase. DEN and other N-nitroso compounds are thought to exert their carcinogenicity via alkylation of DNA. Thus, the measurement of poly(ADP-ribose) and/or its polymerase may provide a basis for measuring DNA damage resulting from carcinogen exposure. (28 Refs)

11. POLYSOMAL POLYADENYLATED RNA AND ALBUMIN MESSENGER RNA IN MASTOMYS LIVER AND IN A CHEMICALLY INDUCED HEPATOCELLULAR CARCINOMA.

Krieg L, Krause-Leipholdt D, Wayss K, Volm M
Institut fur Experimentelle Pathologie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld, D-6900 Heidelberg, W. Germany
Cancer Res; 42(5):1986-1993 1982

A hepatocellular carcinoma line (H78) was established from a primary liver tumor induced in Mastomys natalensis by a single administration of dimethylnitrosamine. Six to 8 mo after transplantation (passages 5 to 7), well-differentiated tumors, still containing glycogen-storing cells, were isolated and used for the preparation of RNA. Polysomal polyadenylated RNAs from Mastomys liver and from the H78 tumor line were then compared by hybridization kinetics. Total kinetic complexities were 6.6 x 10(9) and 6.3 x 10(9) daltons for liver and tumor, respectively. Complexities of the high and middle abundant class were reduced in the hepatoma. Heterologous hybridization reactions revealed that, in terms of RNA ma ss, all or most of the polysomal polyadenylated RNA present in the liver was also present in the tumor and vice versa. However, shifts in the relative abundance of messenger RNA sequences were detected. In contrast to most other transplanted hepatomas, H78 has approx the same content of albumin messenger RNA on its polysomes as has untreated liver. (Author abstract) (44 Refs)

12. CHARACTERIZATION OF THE CONSTITUENT FATTY ACIDS IN THE PHOSPHOGLYCERIDES OF CHEMICALLY INDUCED POLYCYSTIC DISEASE AND GASTRIC TUMOR IN RAT.

Ryuzaki M, Ohta A, Oshima M
Dept. Biology, Kitasato Univ. Sch. Medicine, Sagamihara, Kanagawa 228, Japan
Dev Growth Differ; 23(5):507-513 1981

The positional distribution of fatty acids in choline phosphoglycerides and other phospholipids in hepatoma and other tumors is different from distribution in corresponding normal tissues; this difference may be due to changes in positional distribution of fatty acids in membrane phospholipids. One year old BN rats of both sexes received tap water containing 0.009% N-methyl-N'-nitro-N-nitrosoguanidine to induce polycystic disease or gastric tumors. After 10 mo, whole livers and whole stomachs of experimental and control rats were analyzed for phospholipid classes. In diseased rats, choline phosphoglyceride was about one half that of normals; sphingomyelin content was increased in diseased livers. With regard to composition of fatty acids at the 1-position, diseased livers showed an increase of approx 22% in 16:0 fatty acid and a decrease of approx 12% in 18:1 fatty acid. In diseased organs, fatty acids at the 2-position showed greater saturation. An increase in 15:0 fatty acid at the 2-position of ethanolamine phosphoglycerides was observed in diseased organs. (18 Refs)

13. EXPERIMENTALLY INDUCED TUMORS USED FOR ANGIOGRAPHIC ESTIMATION OF EMBOLIZATION AND CYTOTOXIC TREATMENT.

Strecker EP, Kraus W, Fiebig HH, Kauffmann G, Hauenstein KH
Rontgenabteilung, Diakonissen-Krankenhaus, D-7500 Karlsruhe-Ruppur, W. Germany
Radiologe; 22(2):92-97 1982

Suitability of chemically induced rat tumors and of human tumor (HT) transplanted into nude mice for angiographic estimation of embolization and cytotoxic treatment was investigated. Twenty 4-5-wk-old Wistar rats (100 g body wt) were injected ip with 30 mg/kg dimethylnitrosamine (DMN). Twelve rats developed tumors palpable 35 wk after DMN administration. Angiography revealed cystic formations in both kidneys. Macroscopic expansion of transplanted HT indicated the degree of cytostatic efficiency. Tumor microangiograms were investigated for tumor specific vascular patterns and their changes after cytostatics administration. Ten various HT were transplanted ip into 48 mice. Microangiograms demonstrated a close similarity with angiograms of corresponding HT. Colorectal carcinomas and rhabdomyosarcoma revealed less v ascularity. Angiograms did not change even after several generations. Histological changes could not be detected. Only in stomach cancer and sigma-carcinoma in animals treated with cytostatics, a macroscopic reduction in size could be achieved. Angiography revealed a slight increase in the number of small vessels. Experimental conditions for the nude mice model are more complicated, but HT can be transplanted with a growth rate up to 85%. (27 Refs) (In GER)

14. THE PERSISTENCE OF DNA DAMAGE IN THE PANCREAS OF SYRIAN GOLDEN HAMSTERS TREATED WITH N-NITROSOBIS(2-OXOPROPYL)AMINE.

Lawson T, Hines L, Helgeson S, Pour P
Eppley Inst. for Res. in Cancer, Univ. Nebraska Medical Center, 4315 Dewey Ave., Omaha, NE, 68105
Chem Biol Interact; 38(3):317-323 1982

DNA damage was estimated in the liver, pancreas and salivary gland of Syrian hamsters given N-nitrosobis(2-oxopropyl)amine (BOP) by alkaline sucrose gradient centrifugation. A single BOP dose (10 mg/kg) produced in all three tissues extensive DNA damage that was largely repaired in the salivary gland by 4 wk, while in the liver and pancreas, some DNA damage persisted until 4 wk. When higher BOP doses (20 and 40 mg/kg) were used, considerable DNA damage was still evident in the pancreas, but not in the liver at 6 wk. Great-

er damage persisted in hamsters given 40 mg/kg, compared with those administered 20 mg/kg. (Author abstract) (8 Refs)

15. NEOPLASTIC LESIONS IN THE URINARY TRACT OF WISTAR RATS AFTER TREATMENT WITH N-METHYL-N-NITROSOUREA (MNU) AND ARTIFICIAL SWEETENERS.

Soudah B, Green U, Schneider P, Althoff J
Dept. Experimental Pathology, Medizinische Hochschule, Karl-Wiechert-Alle 9, D-3000 Hannover G1, W. Germany
Exp Pathol; 20(4):197-202 1981

The tumor promoting effect of saccharin, sodium cyclamate or calcium carbonate on urinary tract carcinogenesis initiated by N-methyl-N-nitrosourea (MNU) was investigated in female Wistar AF-Han rats. Based on findings from graded sections, neither enhancement nor promotion could be detected. (Author abstract) (13 Refs)

16. CYTOCHEMICAL MARKERS OF BLADDER CARCINOGENESIS.

Wilson PD, Summerhayes IC, Hodges GM, Trejdosiewicz LK, Nathrath WJ
Physiologisches Institut der Universitat Munchen, Pettenkoferstrasse 12, 8 Munchen 2, W. Germany
Histochem J; 13(6):989-1007 1981

Enzyme cytochemical and immunocytochemical techniques were used at the light and electron microscope levels to study the distribution of potential enzyme and antigen markers of chemical transformation in rat and mouse bladders. In in vivo methylnitrosourea-induced rat tumors, alkaline phosphatase (AP) localization was normal on the external surface of the plasma membranes of some cells whereas in others AP was detected only on intracellular membranes. 5'-Nucleotidase (5NU) localization was abnormal in all cells, being seen on endoplasmic reticulum and nuclear membranes only, while in normal bladders only ectoenzyme localization was seen. After tumors were cultured as explants for 15 days, heterogeneity of AP and 5NU localization was seen on the plasma membranes. Enzyme production within some cells was variable while in other cells, only parts of the membrane reacted heavily. A bimodal pattern of AP localization was seen in transformed cell cultures and tumors of mouse bladder derived by in vitro treatment of explants with dimethylbenz(a)anthracene. Cells had either normal ectoenzyme reaction product or abnormal intracellular membrane reaction product. 5NU and adenosine diphosphatase were lost and an Mg.ATPase and a cyclic AMP-independent, calcium-insensitive 'protein phosphatase' were induced in transformed cell cultures. Immunocytochemical study revealed an epithelial antigen in the cytoplasm of both normal and transformed cells which was associated with reticular cytoplasmic ground substance, plasma membrane vesicles and cytoskeletal elements. (29 Refs)

17. CYTOCHEMICAL CHARACTERISTICS OF ISOLATED RAT HEPATOCYTES DURING DIETHYLNITROSAMINE CARCINOGENESIS.

Bykorez AI, Vinarchuk MP, Grinchishin VP
R. E. Kavetskii Inst. Problems of Oncology, Kiev, USSR
Eksp Onkol; 4(1):55-60 1982

Morphological and histochemical changes in the liver during hepatocarcinogenesis were studied in random-bred albino rats subjected to a daily po administration of 0.02% diethylnitrosamine (DENA). Rats received carcinogen for 15 wk. Within different time periods after the initiation of DENA administration, animals were sacrificed, and the isolated hepatocytes were subjected to cytochemical examination. DENA administration resulted in progressive increase of cell polymorphism and cytochemical heterogeneity of hepatocytes. Significant increase of the number of large hepatocytes with large cell nucleus was observed 1 mo after the initiation of DENA administration. Excessive glycogen accumulation and decrease of ATPase activity were first detected 3 wk after the onset of DENA administration. Exposure to DENA did not produce any significant changes in activities of glucose-6-phosphatase, acid phosphatase, acid DNAse, or nonspecific esterase. (32 Refs) (In RUS)

18. MICROSCOPIC DERIVATIVE CYTOSPECTROPHOTOMETRY.

Liu H, Wang Z, Wang F, Zhang Z
Hebei Medical Coll., Shijrazhuang, People's Republic of China
Zhonghua Wuliyixue Zazhi; 3(2):100-102 1981

A cytospectrophotometric technic is described for DNA analysis. Cells for rat liver cancer induced by diethylnitrosamine and those from normal liver were stained with Feulgen stain and their nuclear DNA was determined at 608-620 nanometer. The av nuclear DNA concentration in liver cancer cells was 15.31 + 3.40 while that in normal liver cells was 8.91 + 1.38. The difference was significant . Possible use of this difference in the automatic computerized cytodiagnosis of liver cancer is discussed. (2 Refs) (In CHI)

19. INDUCTION OF GAMMAGLUTAMYLTRANSPEPTIDASE-POSITIVE ALTERED HEPATOCYTIC LESIONS BY COMBINATION OF TRANSPLACENTAL-INITIATION AND POSTNATAL-SELECTION.

Ogawa K, Yokokawa K, Tomoyori T, Onoe T
Dept. Pathology, Sapporo Medical Coll., Sapporo 060, Japan
Int J Cancer; 29(3):333-336 1982

The purpose of this study was to induce in postnatal life the selective growth of altered hepatocytic populations which had been induced in utero by various chemicals. Pregnant rats of a Wistar strain were given a single dose of various chemical carcinogens on the 18th gestational day. From 2 mo postpartum, both the mothers and offspring were given a diet containing 2-acetylaminofluorene (2-AAF) at a concentration of 0.02% for 2 wk. Then, at the end of the 1st wk after the 2-AAF feeding, a two-thirds partial hepatectomy was performed. All the animals were killed 1 wk after the partial hepatectomy and were examined for the incidence of gamma-glutamyltranspeptidase (GGT)-positive altered hepatocytic foci in the liver. The transplacental administration of not only a hepatic carcinogen, diethylnitrosamine (DEN) but also of 7,12-dimethylbenzanthracene (DMBA), which does not usually produce hepatocellular carcinomas in adult rats, induced GGT-positive altered hepatocytes in the liver of the offspring. These hepatocytes grew into grossly visible hyperplastic nodules within a wk after the two-thirds partial hepatectomy. The possible applicability of the transplacental initiation-postnatal selection model for the short-term assay of transplacental carcinogenicity is discussed. (Author abstract) (21 Refs)

20. ALPHA-FETOPROTEIN FORMATION AND BIOCHEMICAL CHANGES IN RAT LIVER DURING N-DIMETHYLNITROSAMINE-INDUCED CARCINOGENESIS.

Dolezhalova V, Stratil P, Simickova M, Cherni S, Rubenchik BL, Pliss MB, Gorban' GP
Inst. Clinical and Experimental Oncology, Brno, Czechoslovakia
Eksp Onkol; 4(1):51-55 1982

The effects of dimethylnitrosamine (DMNA) on the biosynthesis of alpha-fetoprotein (AFP) and liver metabolism were studied in male Wistar rats. Animals received a diet containing 0.01% DMNA for 20 wk. Extremely low blood levels of AFP were detected on wk 3-4, 25-26, and 35-36 after the initiation of DMNA administration. The low blood level of AFP was correlated with small number of hepatocytes containing AFP. AFP-positive hepatocytes were detected during the first wk after DMNA administration. The number of AFP-containing hepatocytes reached the max 30 wk after the initiation of the experiment, ie during the period of tumor development. The increase of deoxycytidylate deaminase activity was correlated with the increase of the proliferative activity of liver cells. Marked decrease of glucose-6-phosphatase was observed throughout the entire period of DMNA administration. DMNA did not change the rate of glycolysis or the activity of key glycolytic enzymes. (20 Refs) (In RUS)

MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS

21. ROLE OF ESTROGENS AS PROMOTERS OF HEPATIC NEOPLASIA.

Wanless IR, Medline A
Dept. Pathology, Toronto Western Hosp., Toronto, Ontario, Canada
Lab Invest; 46(3):313-320 1982

The administration of estrogens to humans has been associated with the development of benign and possibly malignant hepatocellular neoplasms. This study was designed to investigate the mechanism of this association. We present a rat model that demonstrates that stilbestrol (DES) and ethinyl estradiol promote the development of hepatic neoplasms in rats previously initiated with diethylnitrosamine (DEN). Eighty male and 12 female Fischer-344 rats were given a single intraperitoneal injection of either DEN (200 mg/kg of body wt) or saline. Beginning 4 wk after injection, the rats were given an estrogen or corn oil twice weekly for up to 50 wk. Treatments were stopped at the time of sacrifice or 11 to 29 wk prior to sacrifice. Estrogen treatments included high dose DES (5 mg per dose), low dose DES (0.5 mg per dose), and ethinyl estradiol (0.2 mg per dose). Male and female rats given both DEN and high dose of DES developed grossly visible hepatic hyperplastic nodules (mean, 9.1 per liver) after 20 wk of DES. Nodules also developed if the onset of DES treatment was delayed until 28 wk after initiation. Rats given DEN alone or DES alone did not develop nodules after 20 wk. Microscopic hyperplastic foci also developed in rats given DEN plus DES, DES alone, and DEN alone. The foci in rats given DES alone were largely reversible on cessation of estrogen therapy. Mitotic activity in foci and nodules was prominent during estrogen therapy but declined markedly after cessation of therapy. Similar promoting activity of ethinyl estradiol was observed. Low dose DES was not effective in promoting tumor formation. The data indicate that estrogens promote hepatic neoplasia, perhaps by increasing hepatocyte mitotic activity and thereby facilitating the evolution of previously initiated cells into neoplastic clones. Comparison with human disease should be made with caution, especially because the estrogenic dose administered was approx 200-fold the usual contraceptive dose in humans. However, the analogy between this model and the development of human oral contraceptive-associated hepatic tumors is evident. It is possible that some women have latent 'initiated' cells that divide faster than the surrounding hepatocytes in response to estrogens. (Author abstract) (29 Refs)

22. ENHANCED EFFECT OF GASTRIN ON RAT STOMACH CARCINOGENESIS INDUCED BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE.

Tahara E, Shimamoto F, Taniyama K, Ito H, Kosako Y, Sumiyoshi H
Dept. Pathology, Hiroshima Univ. Sch. Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734, Japan
Cancer Res; 42(5):1781-1787 1982

This study deals with the effects of gastrin on the incidence of gastric tumors in rats induced by N-methyl-N'-nitro-N-nitrosoguanidine. Inbred Basel-Wistar rats received N-methyl-N'-nitro-N-nitrosoguanidine in drinking water (50 ug/ml for 32 wk) in order to produce gastric carcinoids. A treatment with sc injection of pentagastrin (300 ug/kg, once daily for 4 wk) was started at the beginning of N-methyl-N'-nitro-N-nitrosoguanidine treatment simultaneously, on the 4th, 8th, 16th, and 32nd wk after start of N-methyl-N'-nitro-N-nitrosoguanidine treatment, respectively. At autopsy, from the 55th to 60th wk after start of the experiment, only in the 8th-wk group of gastrin-treated rats was the incidence of gastric carcinoid significantly higher than in the gastrin-untreated group of rats receiving N-methyl-N'-nitro-N-nitrosoguanidine alone. The incidence of adenocarcinoma in the glandular stomach also was high only in the 4th-wk group of gastrin-treated rats. However, these effects could not be seen in other gastrin-treated or untreated groups of rats. The data suggest that gastrin treatment in the early stage of rat stomach carcinogenesis by N-methyl-N'-nitro-N-nitrosoguanidine is effective in increasing the development of gastric tumors. (Author abstract) (21 Refs)

MUTAGENICITY OF NITROSO COMPOUNDS

23. MUTAGENICITY AND ALPHA-HYDROXYLATION OF N-NITROSOPYRROLIDINE AND N-NITROSOPIPERIDINE: A POSSIBLE CORRELATION.

Gilbert PJ, Rollmann B, Rondelet J, Mercier M, Poncelet F
(c/o Poncelet) Laboratoire de Toxicologie et Bromatologie, U. C. L. 72.37, Univ. Louvain Sch. Pharmacy, B. 1200 Brussels, Blegium
Toxicology; 22(4):345-352 1982

The rate of biotransformation of N-nitrosopyrrolidine (NPyrr) and N-nitrosopiperidine (NPip) into 1,4-butanediol (BTD) and 1,5-pentanediol (PTD), respectively, in the presence of liver post-mitochondrial fractions was investigated. Postmitochondrial fractions (S9) were obtained from homogenized rat livers and incubated with the test material. NPyrr and NPip metabolites were determined by gas chromatography. The rates of biotransformation of NPyrr and NPip were optimal after 2 hr. The quantity of BTD produced was positively correlated with the concentration of NPyrr (0-10 umole/0.1 ml) in the mixture. BTD concentrations detected in the presence of a sensitive Salmonella strain was lower, but

still positively correlated with NPyrr concentration. Both mutagenicity and metabolism of NPYrr were related to the concentration of S9 liver fractions and required the presence of disodium salt (NADP). With NPip a similar correlation was observed between the mutagenic activity and dose of PTD undetected in the presence of sensitive Salmonella. The metabolic mechanism for NPyrr and NPip is apparently an NADPH-dependent alpha-hydroxylation by which the cyclic nitrosamines were converted into mutagenic intermediates. (12 Refs)

24. COMPARISON OF MUTAGENICITY AND CHEMICAL PROPERTIES OF N-METHYL-N'-ALKYL-N-NITROSOUREAS.

Isobe M, Yano K
Dept. Chemistry, Saitama Medical Sch., 981 Kawakado, Moroyama, Iruma-gun, Saitama 350-04, Japan
Mutat Res; 93(1):57-66 1982

Eleven N-methyl-N'-alkyl-N-nitrosoureas were tested for mutagenicity in Salmonella typhimurium strain TA1535. Mutagenicity was much greater for compounds with a cyclic N'-alkyl group than for those with a chain N'-alkyl group. The greatest mutagenicity was obtained with N-methyl-N'-cyclobutyl-N-nitrosourea. Mutagenicity was slightly correlated with decomposition rate but not with alkylating activity. Results suggest that mutagenicity is strongly related to the structure of N'-alkyl groups. (40 Refs)

25. THE EFFECT OF LIVER POSTMITOCHONDRIAL FRACTION CONCENTRATION FROM AROCLOR 1254-TREATED RATS ON PROMUTAGEN ACTIVATION IN L5178Y CELLS.

Amacher DE, Turner GN
Dept. Safety Evaluation Dept., Pfizer Central Res., Groton, CN, 06340
Mutat Res; 97(2):131-137 1982

Mouse L5178Y/TK+/- cells (strain 3.7.2C) were exposed to N-acetyl-2-aminofluorene (AAF: 50 or 67 ug/ml), 2-aminoanthracene (AA: 0.96 ug/ml), benzanthracene (BA: 7.35 ug/ml), benzo(a)pyrene (BP: 2.5 ug/ml), dimethylnitrosamine (DMN: 74.1 ug/ml), or 3-methylcholanthrene (MCA: 5.4 ug/ml), in the presence of varying concentrations (2.5-10%, vol/vol) of liver S9 postmitochondrial fraction from Aroclor-treated male CD rats. With AAF, AA, BA, BP, and MCA, the occurrence of trifluorothymidine-resistant mutants (TFTr) declined in proportion to increases in the S9 concentration during the 3-hr incubation period. With DMN, the occurrence of TFTr mutants increased moderately in proportion to increases in the S9 concentration during the 3-hr incubation period. The results suggest that two different metabolic events may be involved: activation via non-induced factors (perhaps enzymes) whose activities are totally dependent on the vol of S9 (DMN), and deactivation via induced detoxification pathways in a sequence favored by increasing the S9 concentration (the other promutagens tested). The use of a 'standard' concentration (10%) of rat liver S9 did not seem to provide optimal metabolic activation for any of the promutagens except DMN. With the other promutagens, the greatest degree of activation was observed at the lowest S9 concentration studied. (11 Refs)

26. SUPERMUTAGENICITY OF ETHYLNITROSOUREA IN THE MOUSE SPOT TEST: COMPARISONS WITH METHYLNITROSOUREA AND ETHYLNITROSOURETHANE.

Russell LB, Montgomery CS
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 92(1/2):193-204 1982

The embryotoxicities and mutagenicities of ethylnitrosourea (ENU: 25-100 mg/kg), methylnitrosourea (MNU: 5-7.5 mg/kg), and ethylnitrosourethane (NEC: 100-150 mg/kg) were studied in (C57BL/R1 x multiple-recessive T)F1 mice. Female C57BL/R1 mice were treated with the agent on day 9 or 10 of pregnancy. The spot test was used to obtain information on mutations, cytotoxicity (the occurrence of white midventral spots during the first 7 wk after birth), and teratogenic effects. For all endpoints studied, ENU was more effective than NEC. Compared to MNU, ENU was less toxic, less teratogenic, and less mutagenic in the spot test but more mutagenic in spermatogonia and a much stronger transplacental carcinogen than MNU. MNU is apparently a stronger inducer of gross chromosomal damage than ENU, whereas ENU causes more gene mutations than MNU. Both types of mutational damage are evident on the spot test; gene mutations are evident from spermatogonial studies. (20 Refs)

27. CYTOTOXICITY AND MUTAGENICITY OF DIMETHYLNITROSAMINE IN MAMMALIAN CELLS (CHO/HGPRT SYSTEM): ENHANCEMENT BY CALCIUM PHOSPHATE.

O'Neill JP, Machanoff R, San Sebastian JR, Hsie AW
Biology Div., Oak Ridge Natl. Lab., P.O. Box Y, Oak Ridge, TN, 37830
Environ Mutagen; 4(1):7-18 1982

Conditions for use of the metabolic activator, S9, in Chinese hamster ovary (CHO) cells were studied in the hypoxanthine-guanine phosphoribosyl transferase system to quantify the mutagenicity of dimethylnitrosamine (DMN). The S9 protein was obtained from liver of Aroclor 1254-induced Sprague-Dawley rats. DMN (5 mg/ml) added to cultures of CHO cells, increased both cytotoxicity and mutagenicity with addition of S9, and each increased with increasing amounts of S9; without S9 there was no activity. A previous observation that CaCl2 led to increased cytotoxicity and mutagenicity was verified by addition to the incubation mixture of 10 milliM (mM) MgCl2, 10 mM CaCl2, or both. The greatest increase in activity was observed when both CaCl2 and MgCl2 were included. A precipitate was formed in both the S9 mix and the incubation medium at all concentrations of CaCl2, which resulted in increased activity of DMN (ie, 2.5-10 mM). Since formation of a calcium phosphate precipitate seemed the most likely explanation, the effect of added sodium phosphate was investigated. Maximum activity was obtained with addition of 50 mM sodium phosphate in addition to 10 mM CaCl2 and 10 mM MgCl2. DMN activity increased with increased amounts of S9 protein over the range 0.3-3.0 mg/ml in the S9 mix. The mutagenicity of DMN can be described as 110 mutants/10(6) cells per mM DMN per mg/ml S9 protein per hour. (20 Refs)

28. DIFFERENCES IN TEMPORAL ASPECTS OF MUTAGENESIS AND CYTOTOXICITY IN CHINESE HAMSTER CELLS TREATED WITH METHYLATING AGENTS AND THYMIDINE.

Peterson AR, Peterson H
Cancer Center, Dept. Microbiology, Univ. Southern California, Cancer Res. Lab., 1303 N. Mission Road, Los Angeles, CA, 90033
Proc Natl Acad Sci USA; 79(5):1643-1647 1982

Equitoxic concentrations of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and methyl methanesulfonate (MeMes) produced different frequencies of 5-azaguanine-resistant mutants and different amounts of N7-methylguanine, O6-methylguanine (m6G), and N3-methyladenine in the DNA of V79 Chinese hamster cells. Thus, neither the cytotoxicities nor the mutagenicities of these methylating agents could be attributed solely to nitrogen or to oxygen methylations in the DNA. However, MNNG produced 12-fold more m6G and 5-fold more mutants than did MeMes, indicating that a substantial part of the MNNG-induced mutations resulted from m6G-thymine mispairing during DNA replication. The expression as mutants of mutagenic oxygen methylations in the DNA of cells treated with MNNG was enhanced by thymidine (dThd) and deoxycytidine (dCyd), but these nucleosides did not significantly enhance MeMes-induced mutagenesis. The cytotoxicities of MNNG and MeMes were also increased by 10 uM dThd in proportion to the amount of m6G in the DNA. These increases in cytotoxicity were abolished by dCyd, which did not greatly reduce the dThd-induced enhancements of mutagenesis. Moreover, when dThd was present only during the 2-hr treatment with MNNG, maximal cytotoxicity occurred, but MNNG-induced mutagenesis was not increased. Maximal mutagenesis occurred when the dThd was present throughout the first doubling time of the MNNG-treated cells. Thus, the expression of the cytotoxicity and the mutagenicity associated with m6G in the DNA of V79 cells occurred by quite different mechanisms. (Author abstract) (31 Refs)

29. ON THE NATURE OF PARTIAL LOSSES OF THE Y CHROMOSOME FROM TREATMENT OF RING-X/ BSYY+ MALES WITH DIETHYLNITROSAMINE (DEN) OR PROCARBAZINE AND MATING WITH REPAIR-DEFICIENT ST MUS302 FEMALES OF DROSOPHILA.

Zimmering S, Kammermeyer KL
Div. Biology and Medicine, Brown Univ., Providence, RI, 02912
Mutat Res; 104(1-3):121-123 1982

The nature of partial losses of the Y chromosome after treatment with diethylnitrosamine (DEN) or procarbazine (PCARB) was studied in Drosophila melanogaster. Xc2,yf/ BSYy+ males approx 24 hr old were starved for 6 hr. They were then left untreated or treated with 10 milliM (mM) DEN or 5 mM PCARB. Treated and untreated males were then mated with y as sc;st mus302 females. F1 progeny were classified as regular females (y), regular males (sc B), loss of X or Y (principally loss of ring-X: y ac sc male), loss of BS (sc male), loss of y+ with loss of ac+ (y ac sc B male), loss of y+ without loss of ac+ (y sc B). Loss of y+ was accompanied by loss of ac+ in 15/16 losses produced by DEN and 50/50 losses produced by PCARB. All y ac sc B males showed reduction in eye size consistent with homozygous BS phenotype, indicating interchange of Y-arms. Crosses of ring-X/BSYy+ males with RM(1)y2,su-wa wa bb/o;st mus302 females produced six females carrying the BSY fragment. The BSY fragment was placed in combination with an X.Y chromosome and tested for wild-type alleles of ac and lethal259. One fertile male was obtained; no evidence of either wild-type allele was found. Two fertile males carrying the X.Y/BSY fragment were obtained from crosses of ring-X/BSYy+ males treated with DEN and X.Y,y/y w;st mus302 females. Neither of these males showed evidence of the wild-type alleles. Three other losses of y+ were accompanied by loss of adjacent markers. Thus 18/19 losses of y+ after DEN treatment were apparently produced by chromosome breakage. All or nearly all partial losses of the BSYy+Y chromosome after treatment with DEN or PCARB were attributed to chromosomal breakage. (10 Refs)

30. RELATION BETWEEN THE SOMATIC TOXICITY OF DIMETHYLNITROSAMINE AND A GENETICALLY DETERMINED VARIATION IN THE LEVEL AND INDUCTION OF CYTOCHROME P450 IN DROSOPHILA MELANOGASTER.

Hallstrom I, Magnusson J, Ramel C
Div. Toxicology Genetics, Wallenberg Lab., Univ. Stockholm, Stockholm, Sweden
Mutat Res; 92(1/2):161-168 1982

Enzyme induction and metabolism in Drosophila were studied with the use of somatic toxicity of dimethylnitrosamine (DMN). The activity of cytochrome P450 (P450) in insecticide-resistant Drosophila melanogaster (Hikone R and 5H5 strains) was higher than the P450 activity of insecticide-sensitive strains. Phenobarbital (PB) induced P450 in the sensitive strains but not in the resistant strains. The toxicity and mutagenicity of DMN and the uptake of vinyl chloride (VC) were higher in the resistant strains than in the sensitive strains. The correlation between DMN toxicity and the metabolic differences between the insecticide-resistant and sensitive strains was demonstrated by the increased toxicity of DMN after PB pretreatment in the sensitive strains but not in the resistant strains. A dominant gene, responsible for the patterns of VC and presumably DMN metabolism and the non-inducibility of P450 in the Hikone R strain, was located in region 66 cM of chromosome 2, near the vg gene. This gene may be the major gene responsible for the insecticide resistance of the strain. Genetic variation in the mixed function oxidase system associated with insecticide resistance in Hikone R does not apply to the enzyme system as a whole. Benzo(a)pyrene monooxygenase activity and inducibility are the same in the insecticide-sensitive and Hikone R strains of Drosophila. (12 Refs)

31. N-METHYL-N'-NITRO-N-NITROSOGUANIDINE SENSITIVITY OF E. COLI MUTANTS DEFICIENT IN DNA METHYLATION AND MISMATCH REPAIR.

Jones M, Wagner R
Departement de Biologie Moleculaire, Universite Libre de Bruxelles, rue des Chev aux 67, B-1640 Rhode St Genese, Belgium
MGG; 184(3):562-563 1981

E coli mutants deficient in DNA methylation (dam) and mismatch repair (mut) have been characterized with respect to their sensitivity to N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). Dam bacteria are more sensitive than mutH, mutL, and mutS single mutant bacteria. Dam mutL and dam mutS double mutant bacteria are less sensitive than dam bacteria, whereas dam mutH double mutant bacteria are as sensitive as dam bacteria. This pattern of MNNG sensitivity may be a result of the specificity of the components of the E coli mismatch repair system. (Author abstract) (6 Refs)

32. ISOLATION OF FLUOROPYRIMIDINE-RESISTANT MURINE LEUKEMIC CELL LINES BY ONE-STEP MUTATION AND SELECTION.

Mulkins MA, Heidelberger C
(c/o Heidelberger), Univ. Southern California, Comprehensive Cancer Center, Los Angeles, CA, 90033
Cancer Res; 42(3):956-964 1982

The effectiveness of the clinically useful fluoropyrimidines in the treatment of human cancer is often limited by the development of resistance to the drugs by the tumor. In order to systematically study the mechanisms of resistance to 5-fluorouracil and its nucleoside derivatives, several cell line resistant to these drugs have been derived from murine leukemia cells by a one-step mutation and selection procedure. Logarithmically growing suspension cultures of L1210 and P388 cells were treated with ethyl methanesulfonate, N-methyl-N'-nitro-N-nitrosoguanidine, or ICR-191 at concentrations which result in 20 to 30% cell survival. After a 10-day expression time, mutagenized cells were plated into soft-agarose medium that contained 10(-5) M 5-fluorouracil, 10(-5) M 5-fluoro-2'-deoxyuridine or 10(-6) M 5-fluorouridine. Twenty stable clones were isolated and found to be 5-to 28-fold resistant to growth inhibition by 5-fluorouracil, 4,000-to 25,000-fold resistant to 5-fluoro-2'-deoxyuridine, or 8-to 220-fold resistant to 5-fluorouridine. The clones retain their drug-resistant phenotype after repeated passaging in the absence of selection. Since the biochemical changes responsible for resistance to one drug can render the cells collaterally sensitive to other drugs, the growth-inhibitory effects of antimetabolites that inhibit other steps in pyrimidine metabolism were examined in the wild-type cells and in the fluoropyrimidine-resistant sublines. Although cross-resistance to 5-azacytidine was found in L1210 cells selected for resistance to 5-fluorouridine, none of the cell lines tested demonstrated collateral sensitivity to methotrexate, 1-beta-D-arabinofuranosylcytosine, 5-azacytidine, or N-(phosphonacetyl)-L-aspartate. (Author abstract) (38 Refs)

33. INDUCTION OF 6-THIOGUANINE-RESISTANT MUTATIONS BY RAT-LIVER HOMOGENATE (S9)-ACTIVATED PROMUTAGENS IN HUMAN EMBRYONIC SKIN FIBROBLASTS.

Chen DJ, Okinaka RT, Strniste GF, Barnhart BJ
Genetic Group, LS-3, MS886, Los Alamos Natl. Lab., Los Alamos, NM, 87545
Mutat Res; 101(1):87-98 1982

A quantitative mutation assay consisting of early passage of cultured human fibroblasts together with an exogenous rat-liver microsomal preparation to activate promutagens capable of inducing cytotoxic and mutagenic responses is described. Optimal conditions for a 6-thioguanine (6-TG) resistance mutation assay in the diploid human embryonic skin fibroblast strain (GM10) were investigated. The promutagens used were benzo[a]pyrene (BaP), 3-methylcholanthrene (3MC), and dimethylnitrosamine (DMN). At a constant amount of S9 protein concentration, a linear correlation between mutagenicity and dose was observed. At 50% survival, the mutation frequencies of BaP and 3MC (5 ug/ml) were 60 and 30x the background frequency, respectively, and DMN (5 mg/ml) induced 6-TG mutant frequencies 25x more than background. 3MC and BaP (5 ug/ml) decreased the colony-forming ability of GM10 to 50 and 20%, respectively; DMN at concentrations of 1 and 5 mg/ml inhibited colony-forming ability between 20 and 60%. At high S9 concentrations, a deactivation or detoxification phenomenon was observed. When the mutagenic efficiency of S9-activated chemicals was plotted as the number of induced mutations vs log survival it was not affected by the deactivation capacity of S9 proteins. (42 Refs)

34. INDUCTION OF CHROMATID BREAKAGE BY CLASTOGENS IN CELLS OF G2 PHASE.

Hsu TC, Cherry LM, Pathak S
Dept. Cell Biology, Univ. Texas M. D. Anderson Hosp. and Tumor Inst. at Houston, Houston, TX, 77030
Mutat Res; 93(1):185-193 1982

Clastogenicity of several compounds was tested in cultures of human peripheral blood cells in G2 phase. Cells were exposed simultaneously to Colcemid and actinomycin D (AMD: 2.8 uM for 15, 30, 45, or 60 min or 2.8, 1.4 or 0.28 uM for 60 min). Chromosome breakage was induced in a dose-dependent manner. The most frequent aberrations were chromatid breaks; chromatid exchanges were rare. In a modified procedure, cells were exposed to 2.8 uM AMD for 90 min, but to Colcemid for only the last 60 min. Among 100 metaphase figures 95% had chromatid breaks; the av number of breaks/cell was 3.77. Autoradiographic studies indicated that all chromatid aberrations occurred during G2 phase. Additional clastogens were tested at 100 uM concentrations (or at lower concentrations when 100 uM was too toxic). Chromatid breaks were produced by adriamycin, bleomycin, neutral red, gentian violet, and 1,4-dihydroxy-5,8- *[2-(2 hydroxymethyl)amino]ethylamino* -9,10-anthracenedione at 15-100x the frequency produced in controls. No increases in the frequency of chromatid breaks were produced by mitomycin C, hydroxyurea, ethidium bromide, or cytosine arabinoside. Cis-platinum II produced borderline results. N-Methyl-N'-nitrosoguanidine was mildly clastogenic in G2 phase. Results indicate that a simple protocol can be used to determine clastogenicity in G2-phase cells. (8 Refs)

CELLULAR EFFECTS OF NITROSO COMPOUNDS

35. QUANTITATIVE DOSE-RESPONSE RELATIONS FOR THE CYTOTOXIC ACTIVITY OF CHLOROETHYLNITROSOUREAS IN CELL CULTURE.

Weinkam RJ, Deen DF
Dept. Medicinal Chemistry, Purdue Univ., West Lafayette, IN, 47907
Cancer Res; 42(3):1008-1014 1982

A dose-response relation for the cytotoxic activity of chloroethylnitrosourea cancer chemotherapeutic agents in cell culture has been developed. Data for the activity of 1,3-bis(2-chloroethyl)-1-nitrosurea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, 1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1 nitrosourea, and 1-(2-chloroethyl)-3-(piperidine-3,6-dion-3-yl)-1 nitrosourea against 9L rat brain tumor cells are presented. Cytotoxicity resulting from treatment schedules at different initial drug concentrations, exposure periods, and preincubation periods are correlated using a proposed dose function. Equations are presented that incorporate drug concentration, duration of exposure of cells, and the rate constant for conversion of the drug from an active intermediate into a single dose function. When compared in this way, all cell treatment schedules used were found to be equally effective in killing cells in culture. The cytotoxic activities of the four different chloroethylnitrosourea analogs were also found to be the same. These data demonstrate the application of quantitative dose-response relations to the activity of chloroethylnitrosoureas in cell culture and provide new insight into the mechanism of action and structure-activity relationships of these compounds. (Author abstract) (52 Refs)

36. HETEROGENEOUS CHEMOSENSITIVITIES OF SUBPOPULATIONS OF HUMAN GLIOMA CELLS IN CULTURE.

Yung WK, Shapiro JR, Shapiro WR
(c/o Shapiro), Cornell Univ. Medical Coll., 1275 York Ave., New York, NY, 10021
Cancer Res; 42(3):992-998 1982

Six karyotypically distinct clonal cell lines isolated from each of two freshly resected human malignant gliomas were examined for heterogeneity of morphology, in vitro growth rate, and chemosensitivity to 1,3-bis(2-chloroethyl)-1-nitrosourea and cis-diamminedichloroplatinum (II). Each clone was identified karyotypically as having come from the parent tumor. The karyotypic deviations were primarily numerical; chromosome numbers ranged from hypodiploid to near-tetraploid. Three morphological types were recognized: astrocyte-like; squamous-like; and fibroblast-like. The growth rates differed among the clones; the doubling times ranged from 48 to 84 hr in those from one tumor and from 72 to 252 hr in the other. Chemosensitivity was measured by cytotoxicity and/or colony-forming assay. In both assays and in both tumors, heterogeneity of chemosensitivity response to both drugs was demonstrated among the different clones from the same tumor. Dose-response curves from some clones differed statistically (log-probit analysis) from those of others, and when the curves were parallel, their 50% effective doses often differed. For the cytotoxicity assay, the 50% effective doses for BCNU ranged from 43 to 94 ug/ml and for cis-diamminedichloroplatinum (II), from 29 to 340 ug/ml. For the colony-forming assay, the 50% effective doses for 1,3-bis(2-chloroethyl)-1-nitrosourea ranged from 4.5 go 7.0 ug/ml and for cis-diamminedichloroplatinum (II), from 0.35 to 1.40 ug/ml. No correlation was evident between the chromosome number, morphology, growth rates, or chemosensitivities of the clones. These results identified heterogeneity of chemosensitivity among cellular subpopulations in human malignant gliomas. (Author abstract) (20 Refs)

37. CYCLIC NUCLEOTIDE MODULATION OF IN VITRO MORPHOLOGICAL TRANSFORMATION OF SYRIAN HAMSTER CELLS.

Mironescu SG, Epstein SM, DiPaolo JA
Dept. Pathology, Univ. South Carolina Sch. Medicine, Columbia, SC, 29208
Cancer Res; 42(4):1274-1278 1982

The cyclic nucleotides, cyclic adenosine 3':5'-monophosphate (cAMP) and cyclic guanosine 3':5'-monophosphate (cGMP) or their dibutyryl and monobrominated derivatives, may either increase or decrease morphological transformation of Syrian hamster embryo cells exposed to N-methyl-N'-nitro-N'-nitrosoguanidine (MNNG). The effect on transformation is primarily a function of the parent cyclic nucleotide and the duration of exposure to the nucleotides. At concentrations of 5 mM or larger for a minimum 24-hr exposure cAMP, cGMP, and their congeners reduced the colony-forming ability of non-transformed Syrian hamster embryo cells not exposed to MNNG; however, cGMP and its derivatives caused less toxicity than cAMP or its analogs. cAMP and its monobrominated and dibutyrylated derivatives decreased the transformation frequency associated with MNNG irrespective of whether the various adenylnucleotides were administered before or after MNNG. The greatest inhibitory effect on MNNG-induced transformation was obtained with N6,O2-dibutyryl cyclic adenosine 3':5'-monophosphate followed in order by 8-bromocyclic adenosine 3':5'-monophosphate and cAMP. At equimolar doses, the dibutyryl and brominated analogs of cGMP but not unsubstituted cGMP enhanced transformation when administered prior to exposure of the Syrian hamster embryo cells to MNNG but reduced the transformation frequency when added after MNNG. The enhancing and inhibitory effects of the guanine cyclic nucleotide-induced alteration of MNNG-associated transformation frequencies were dose and time dependent and occurred in the order N6,O2-dibutyryl cyclic guanosine 3':5'-monophosphate greater than 8-bromocyclic guanosine 3':5'-monophosphate very much greater than cGMP. Butyric acid neither diminished nor increased MNNG-induced transformation frequency. The latter suggests that butyrate ions formed by metabolism of the cyclic nucleotide analogs were not a factor in the observed alterations of transformation frequency. (Author abstract) (35 Refs)

38. UNSCHEDULED DNA SYNTHESIS INDUCED BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE IN HELA CELLS.

Yamada K, Kato H, Hanaoka F, Yamada M
(c/o Hanaoka) Dept. Physiological Chemistry, Univ. Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113, Japan
Gan; 73(1):63-69 1982

N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced repair (unscheduled) DNA synthesis was studied in intact HeLa cells as well as in the cell lysate. The incorporation of dTTP[methyl-3H] in vitro by the cell lysate was dependent on the dose of MNNG, and was linear for 2 min, reaching the maximum at 4 min. The optimum conditions were the same as for UV-induced in vitro repair synthesis. The presence of hydroxyurea and arabinofuranosyl cytosine during in vivo incubation with MNNG was necessary for enhancement of in vitro DNA synthesis. This MNNG-induced in vitro DNA synthesis was inhibited by aphidicolin, but not by 2',3'-dideoxythymidine-5'-triphosphate. It thus appears that DNA polymerase alpha participates in MNNG-induced unscheduled DNA synthesis in vitro. (Author abstract) (25 Refs)

39. INACTIVATION OF NUCLEOTIDE EXCISION REPAIR IN CHINESE HAMSTER OVARY CELLS BY EXPOSURE TO AN ALKYLATING AGENT.

Park SD, Cleaver JE
(c/o Cleaver) Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Photochem Photobiol; 35(3):419-421 1982

Unscheduled DNA synthesis and excision of pyrimidine dimers in Chinese hamster ovary cells irradiated with UV light were inhibited by prior exposure to the alkylating agent N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) (1-10 uM). Although the pathways for excision of pyrimidine dimers and alkylation damage are known to differ, alkylations from MNNG exposure appear to have a direct effect on the nucleotide excision repair system. These results indicate that the method of exposing cells to two DNA-damaging agents to determine whether they are repaired by common or different pathways can be quite unreliable because of other effects on the repair systems themselves. (Author abstract) (27 Refs)

40. BUTYRATE DOES NOT INDUCE SINGLE STRAND BREAKS IN FRIEND ERYTHROLEUKEMIA CELLS OR IN 3T6 MOUSE FIBROBLASTS.

Wintersberger E, Mudrak I
Institut fur Molekularbiologie, Universitat Wien, Wasagasse 9, 1090 Wien, Austria
FEBS Lett; 139(2):218-220 1982

DNA breakage by the fatty acid sodium butyrate (SB) was studied. Fibroblasts from 3T6 mice (3T6FB) and Friend erythroleukemia cells (FEL) were grown separately in vitro. After labeling with [3H]thymidine cultures were exposed to various concentrations of SB or dimethyl sulfoxide (DMSO) for various times up to 24 hr, or to N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) for 30 min. DNA was extracted and analyzed by alkaline extraction. No differences were found between DNA from untreated 3T6FB and DNA from 3T6FB treated with SB for 2, 4, or 6 hr at concentrations that produced blockage of cells in G1 phase after 20-24 hr exposure. MNNG produced single strand breaks at concentration of 0.05 millimoles/liter (mM/l). No single strand DNA breaks were produced in FEL by SB at a concentration (2 mM/l) which produced optimal terminal differentiation. Similar results were obtained with 3% DMSO. MNNG produced single strand breaks in DNA of FEL at a concentration of 0.01mM/l. Results indicate that, at concentrations that allow the cells to proceed through terminal differentiation, neither SB nor DMSO produces single strand breaks in DNA of 3T6FB or FEL. (20 Refs)

41. MOLECULAR DOSIMETRY OF DNA DAMAGE CAUSED BY ALKYLATION. I. SINGLE-STRAND BREAKS INDUCED BY ETHYLATING AGENTS IN CULTURED MAMMALIAN CELLS IN RELATION TO SURVIVAL.

Abbondandolo A, Dogliotti E, Lohman PH, Berends F
(c/o Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 92(1/2):361-377 1982

In cultured Chinese hamster cells, N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG), N-ethyl-N-nitrosourea (ENU), ethyl methanesulfonate (EMS), and diethylsulfonate (DES) differed markedly in their induction of DNA single-strand breaks (SSB) and alkali-labile sites (ALS) when the doses were compared on a molar basis (ENNG was about 1,000x more active than the other ethylating agents), but the agents were about equally effective in inducing SSB and ALS when doses of equal cytotoxicity were used. Prolonged alkali exposure greatly increased the number of SSB. DNA from untreated cells formed SSB slowly for about 10 hr; the rate then increased, remaining constant for up to 40 hr. Cells exposed to the ethylating agents showed an accelerated, dose-dependent linear generation of SSB for 10 hr, followed by a short plateau, followed by renewed SSB formation at a constant rate which was somewhat higher than the rate observed in untreated cells. The initial phase of SSB formation was attributed to phosphotriester hydrolysis; the causes of the later phase were unidentified. Zero intercepts seemed to be a measurement of the intracellular formation of apurinic sites. The kinetics of SSB induction as a function of lysis time (1 or 21 hr) were compared for ENNG and DES. A 24-hr repair period before lysis reduced the intercept phenomenon in cells exposed to ENNG but not DES. Since DES degraded rapidly during the 1-hr exposure period, most of the 'apurinic-site' damage was induced in the initial phases of exposure and may have been repaired at its end. The types of d amage observed (reparable and nonreparable apurinic sites and phosphotriesters) seemed to be of little consequence for cell survival. (26 Refs)

42. POTENTIATION OF CELL KILLING BY INHIBITORS OF POLY(ADP-RIBOSE) POLYMERASE IN FOUR RODENT CELL LINES EXPOSED TO N-METHYL-N-NITROSOUREA OR UV LIGHT.

Durrant LG, Boyle JM
Paterson Lab., Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England
Chem Biol Interact; 38(3):325-338 1982

The sensitivities (Do-values) of the cytotoxic effect of MNU on four rodent cell lines were: mouse L1210, 0.07 mM; rat Yoshida sarcoma, 0.52 mM; Chinese hamster V79A, 0.70 mM and the UV sensitive, x-ray sensitive V79/79, 0.35 mM. The abilities of maximum non-toxic doses of the poly(ADP-ribose) polymerase inhibitors, 5-methyl nicotinamide (5MeN), 3-methoxybenzamide (3MBA) and caffeine to potentiate this cytotoxicity and that of UV light in V79A and V79/79 was measured. The degree of potentiation (ratio Do without inhibitor/Do with inhibitor) was both agent and cell line dependent. In general the lymphoid cell lines L1210 and YS showed greater potentiation, up to four-fold, than did the fibroblast lines V79A and V79/79. The use of inhibitors in pairs suggested that 5MeN and 3MBA affect one process whereas caffeine affects additional processes. The data provide further support for a role for poly(ADP-ribose) in DNA repair, but indicate that metabolic factors may modify the effectiveness of individual inhibitors of poly(ADP-ribose)polymerase in different cell lines. (Author abstract) (40 Refs)

43. PRIMARY CULTURE OF PRENEOPLASTIC HEPATOCYTES FROM RATS TREATED WITH 2-ACETYLAMINOFLUORENE AND CLOFIBRATE: RELATIONSHIP BETWEEN RESISTANCE TO DIMETHYLNITROSAMINE AND RESPONSIVENESS OF PEROXISOMES.

Sawada N, Furukawa K, Gotoh M, Mochizuki Y, Tsukada H
Dept. Pathology, Cancer Res. Inst., Sapporo Medical Coll., Minami-1-jo, Nishi-17-chome, Chuo-ku, Sapporo 060, Japan
Gan; 73(1):1-6 1982

Hepatocytes of 2-acetylaminofluorene-induced hyperplastic nodules of rats treated with clofibrate were transferred to primary culture after dispersion by a collagenase perfusion technique. After 48-hr treatment with dimethylnitrosamine (DMN), the resistance to the agent of the cells forming rod-shaped peroxisomes was examined. Catalase activity of the DMN-resistant cells was also determined. At concentrations of 10(-3) M and 10(-4) M DMN, the resistant cell population of hepatocytes with rod-shaped peroxisomes was larger than that of the cells without abnormal peroxisomes. On the other hand, the catalase activity of the attached cells that remained after DMN treatment decreased as the concentration of DMN was increased. The cells showing a stronger induction of the enzyme activity were found to be more sensitive to the cytotoxicity of DMN and they became detached from the culture dishes. (Author abstract) (21 Refs)

44. PROPERTIES OF HUMAN MELANOMA CELLS RESISTANT TO 5-(3',3'-DIMETHYL-1-TRIAZENO)IMIDAZOLE-4-CARBOXAMIDE AND OTHER METHYLATING AGENTS.

Parsons PG, Smellie SG, Morrison LE, Hayward IP
Queensland Inst. Medical Res., Herston, Queensland 4006, Australia
Cancer Res; 42(4):1454-1461 1982

In a cloned line of human melanoma cells (MM253c1), the dose of 5-(3',3'-dimethyl-1-triazeno)imidazole-4-carboxamide (DTIC) giving 37% survival was lowered by a factor of 6.8 when mouse liver microsomes were present. MM253c1 sublines resistant to microsome-activated DTIC, 5-(3'-methyl-1-triazeno)imidazole-4-carboxamide (MTIC), or N-methyl-N'-nitro-N-nitrosoguanidine were derived separately by one treatment of the parent line with a highly toxic level of the particular agent. Compared with MM253c1, the sublines had a higher chromosome and DNA content and a high degree of cross-resistance to all of these agents, to N-methyl-N-nitrosourea, and to ethyl methanesulfonate, but less resistance to methyl methanesulfonate and dimethyl sulfate and no resistance to killing by melphalan, UV light, gamma-rays, or light-activated DTIC and its photoproducts. MTIC-induced DNA damage and repair were compared in late-passage MM253c1 and MM253c1-3D, a resistant subline obtained after three cycles of treatment with microsome-activated DTIC. Protein synthesis and, after allowance for pool size effects, nucleotide synthesis were not inhibited by MTIC during the first 12 hr. After 12 hr, inhibition of DNA synthesis occurred and correlated with cell death. The level of DNA repair synthesis induced by MTIC was the same in each line and was much less than that induced by equitoxic UV lights. Sedimentation of DNA in alkaline sucrose revealed one to three breaks/10(8) daltons in both lines during the first 24 hr after a lethal dose of MTIC. MM253c1-3D showed fewer breaks than MM253c1 in the alkaline elution method 4 hr after treatment with 0.06 mM but not with 0.3 mM MTIC. The nucleoid and DNA-unwinding rate methods, detecting a much lower level of spontaneous or enzymically induced breaks, showed immediate dose-dependent formation of breaks, followed by substantial resealing within 1 to 2 hr and complete recovery after 24 hr; no major difference was found between the two lines. (48 Refs)

45. LYMPHOBLASTOID LINES AND SKIN FIBROBLASTS FROM PATIENTS WITH TUBEROUS SCLEROSIS ARE ABNORMALLY SENSITIVE TO IONIZING RADIATION AND TO A RADIOMIMETIC CHEMICAL.

Scudiero DA, Meshell AN, Scarpinato RG, Meyer SA, Clatterbuck BE, Tarone RE, Robbins JH
Frederick Cancer Res. Center, P.O. Box B, Frederick, MD, 21701
J Invest Dermatol; 78(3):234-238 1982

Lymphoblastoid lines, derived by transforming peripheral blood lymphocytes with Epstein-Barr virus, and skin fibroblast lines were established from two patients with tuberous sclerosis. The number of viable lymphoblastoid cells was determined by their ability to exclude the vital dye trypan blue after their irradiation with x-rays or 254 nm ultraviolet light. The growth of fibroblasts was determined by their ability to form colonies after treatment with the radiomimetic, DNA-damaging chemical N-methyl-N'-nitro-N-nitrosoguanidine. The tuberous sclerosis lymphoblastoid lines were hypersensitive to x-rays but had normal sensitivity to the ultraviolet radiation. The tuberous sclerosis fibroblast lines were hypersensitive to the N-methyl-n'-nitro-N-nitrosoguanidine. The hypersensitivity of tuberous sclerosis cells to x-rays and to N-methyl-N'-nitro-N-nitrosoguanidine is believed to reflect defective repair of DNA damaged by these agents and may provide the basis for in vitro, including prenatal, diagnostic tests for tuberous sclerosis. (Author abstract) (51 Refs)

46. MOLECULAR MECHANISM OF ADAPTATION OF CELLS TO LOW LEVELS OF CARCINOGENIC AGENTS.

Villani G
Laboratoire de Pharmacologie et de Toxicologie Fondamentales, CNRS, 205, route de Narbonne, 31078 Toulouse Cedex, France
Pathol Biol (Paris); 30(2):117-123 1982

Adaptation of Escherichia coli, rat liver cells and human fibroblasts to the cytotoxic and mutagenic effects of alkylating agents such as N-methyl-N'-nitro-N-nitrosoguanidine (MMNG), dimethylnitrosamine (DMN), and N-methylnitrosourea (MNUA) are reviewed. Through exposure to low doses of alkylating agents an increased numbers of cells are able to survive the challenge of high doses; fewer mutations are observed among survivors. Adaptation in E coli, a process involving DNA repair, is inducible and non-specific, consisting of two dissociable phenomenon (increased survival, decreased mutagenesis) controlled by gene polA, and is independent of other repair systems. Studies of adaptation to MNNG in E coli have shown that following adaptation, the methyl group is transferred from the O-6 position of guanine to an acceptor protein which is rapidly inactivated. After exposure to a challenge dose of DMN, fewer DNA O-6 methylguanine lesions were found in livers of rats preexposed to low doses of DMN for 4-6 wk as compared with untreated controls; the same number of N-7 methylguanine and N-3 methyladenine lesions were found in both groups. Pretreatment of cultured human fibroblasts with low doses of MNNG or MNNU increased their resistance to challenge; fewer sister chromatid exchanges were observed following the challenge. (41 Refs) (In FRE)

47. EFFECTS ON MOUSE BLASTOCYSTS OF IN VITRO EXPOSURE TO METHYLNITROSOUREA AND 3-METHYLCHOLANTHRENE.

Iannaccone PM, Tsao TY, Stols L
Dept. Pathology, Northwestern Univ. Medical Sch., Chicago, IL, 60611
Cancer Res; 42(3):864-868 1982

Mouse blastocysts were exposed in vitro to various concentrations of N-methyl-N- nitrosourea and 3-methylcholanthrene. The incorporation of [3H]thymidine, [3H]uridine, and [3H]leucine into the exposed blastocysts was determined either immediately following exposure or after 18 hr of culture. The concentrations of N-methyl-N-nitrosourea or 3-methylcholanthrene used had no effect on blastocyst viability in either situation. There was a concentration-dependent decrease in the incorporation of the precursors into blastocysts exposed to N-methyl-N-nitrosourea which appears to be more pronounced after 18 hr in culture. This effect was not demonstrated for 3-methylcholanthrene, which requires metabolic activation for reactivity. Blastocysts exposed to N-methyl-N-nitrosourea were injected into the uterine horns of surrogate mothers; a significant increase in the resorption rate of these blastocysts was seen when compared with controls. Similar experiments were performed to determine birth rate. A dose-dependent decrease in birth rate was observed which correlated well with the effects on incorporation of thymidine, uridine, and leucine but not with the effect on implantation rate. (Author abstract) (17 Refs)

48. DECREASED CYTOTOXICITY OF CIS-DIAMMINEDICHLOROPLATINUM(II) BY ALPHA-DIFLUOROMETHYLORNITHINE DEPLETION OF POLYAMINES IN 9L RAT BRAIN TUMOR CELLS IN VITRO.

Oredsson SM, Deen DF, Marton LJ
(c/o Marton) Editorial Office, Dept. Neurological Surgery, Univ. California, 350 Parnassus Ave., Suite 807, San Francisco, CA, 94117
Cancer Res; 42(4):1296-1299 1982

Before treatment with the cytotoxic drug cis-dichlorodiammineplatinum(II) (cis-platinum), 9L rat brain gliosarcoma cells grown in vitro were depleted of intracellular polyamines by alpha-difluoromethylornithine (DFMO; 10 mM, 48 hr), an enzyme-activated, irreversible inhibitor of the polyamine-synthetic enzyme ornithine decarboxylase. In contrast to studies that showed that the cytotoxicity of 1,3-bis (2-chloroethyl)-1-nitrosourea as measured by colony-forming efficiency is enhanced by DFMO depletion of intracellular polyamines, the cytotoxicity of cis-platinum was significantly decreased in polyamine-depleted 9L cells. At 10, 1, and 0.1% survival levels the dose modification factors were 2.0 to 2.1. Addition of exogenous putrescine to polyamine-depleted 9L cells 24 hr before treatment with cis-platinum partially reversed this phenomenon. When 9L cells were treated either with DFMO and cis-platinum or with DFMO, putrescine, and cis-platinum for 1 hr, a time period that is too short for DFMO to affect intracellular polyamine levels, the cytotoxicity of cis-platinum was decreased, but to a significantly lesser extent than by the 48 hr DFMO pretreatment. Putrescine alone did not alter the cytotoxic effect of cis-platinum when administered either 24 or 1 hr before treatment. DFMO appears to affect cis-platinum cytotoxicity by two different mechanisms, the first mediated through polyamine depletion and the second through a direct interaction with cis-platinum. (Author abstract) (29 Refs)

TRANSPLACENTAL EFFECTS OF NITROSO COMPOUNDS

49. SHORT-TERM TESTS FOR TRANSPLACENTALLY ACTIVE CARCINOGENS. SENSITIVITY OF THE TRANSPLACENTAL MICRONUCLEUS TEST TO DIETHYLNITROSAMINE.

Cole RJ, Taylor N, Cole J, Henderson L, Arlett CF
Developmental Genetics Lab., Sch. Biological Sciences, M.R.C. Cell Mutation Unit, Univ. Sussex, Falmer, Brighton, England
Mutat Res; 104(1-3):165-171 1982

Dose-dependent clastogenic effects of diethylnitrosamine (DEN) in utero were examined using the transplacental micronucleus test. Random-bred albino mice were mated and treated with DEN ip. Frequencies of polychromatic RBC containing micronuclei were determined in preparations of fetal liver and neonatal peripheral blood. The youngest animals investigated were exposed to DEN in utero during days 15-16 of gestation. A small but significant increase in frequency of micronucleated polychromatic RBC (MNPCE) was detectable in fetal liver 36 hr after treatment. A high level of significance was obtained when exposure was initiated during day 17 of gestation. No increases in frequency of MNPCE were observed in maternal bone marrow. Polychromatic RBC derived from fetal liver during the last day of gestation persisted in the circulation of neonatal animals. Therefore, the frequency of MNPCE in smears of peripheral blood can be used to measure clastogenic effects when the metabolic capacity of the prenatal liver is fully expressed. Pregnant animals were treated late on day 17 of gestation and blood smears were prepared from newborn animals 45 hr after beginning exposure. Dose-related increases in frequencies of MNPCE in neonatal mice after in utero exposure were obtained. Variation in response to DEN between members of litters and between litters was greater than observed with other chemicals, suggesting that onset of the ability to metabolize DEN is variable. (28 Refs)

50. REDUCTION OF ETHYLNITROSOUREA-INDUCED NEOPLASTIC PROLIFERATION IN RAT TRIGEMINAL NERVES BY NERVE GROWTH FACTOR.

Vinores SA, Koestner A
Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA, 19111
Cancer Res; 42(3):1038-1040 1982

Ethylnitrosourea administered to pregnant rats on the 21st day of gestation at a dose of 50 mg/kg resulted in early neoplastic proliferation or neurinomas of trigeminal nerves in 90% of the offspring at 90 days of age. Treatment with nerve growth factor either postnatally following ethylnitrosourea administration or transplacentally prior to ethylnitrosourea treatment appeared to result in a reduction of neurinomas at 90 days of age. (Author abstract) (17 Refs)

EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUN DS

51. NITROGEN AS A POTENTIAL HEALTH HAZARD.

Magee PN
Fels Res. Inst., Temple Univ. Sch. Medicine, 3420 North Broad St., Philadelphia, PA, 19140
Philos Trans R Soc Lond [Biol]; 296(1082):543-550 1982

Ways in which disturbances of the nitrogen cycle might result in deleterious effects on human and animal life are discussed. Evidence that nitrites are carcinogenic in rats exists but is controversial. Nitrosamines are powerful carcinogens and mutagens that occur in the environment and can be formed in the body from non-carcinogenic precursors. (33 Refs)

52. TOXICOLOGY OF N-NITROSO COMPOUNDS.

Coulston F, Olajos EJ
Albany Medical Coll., Albany, NY, 12208
Ecotoxicol Environ Saf; 6(1):89-96 1982

Toxicology of N-nitroso compounds is discussed with respect to formation, carcinogenic effect of precursor amino compounds and nitrite, and significance to man. The potential nitrosation of drugs which are amine or amide derivatives or drug metabolic conversion products containing an amino group is of interest. Experimental evidence that N-nitroso compounds can be formed in vivo is reviewed; however, only a few studies have involved nitrosation conditions simulating those in the environment or in actual animal or human conditions. Standardized in vitro nitrosation assays that more accurately define conditions under which biological nitrosation occurs in the mammalian stomach would enhance our knowledge of in vivo nitrosation. The relationship between N-nitrosation, mutagenicity, and carcinogenicity based on previously reported data of relative in vitro nitrosatability of certain drugs, the mutageni-

city of nitrosation products, and the carcinogenicity of the parent compounds when fed to rats concurrently with nitrite is tabulated. Very large differences between nitrosatability of different drugs are evident, establishing the nitrosation assay as a potentially useful screening procedure. A parallel relationship between nitrosatability of various drugs and mutagenicity is demonstrated. Presently, no evidence exists concerning the carcinogenic effect of N-nitroso compounds derived from drugs that are known to undergo nitrosation or to which man has been occupationally exposed. In vitro nitrosation studies have defined potential nitrosatable precursors and the conditions necessary for nitrosation. In vivo tests, with low levels of precursor amino compounds and/or nitrite, reveal levels of N-nitroso derivatives that are not in excess of low background levels. (31 Refs)

53. ESTIMATION OF INHALATION EXPOSURE TO N-NITROSODIPROPYLAMINE DURING THE APPLICATION AND INCORPORATION OF THE HERBICIDE TRIFLURALIN.

Day EW, Saunders DG, Mosler JW, McKinney EM, Powers FL, Griggs RD, Frank R

Lilly Res. Lab., Eli Lilly and Co., Greenfield, IN, 46140

Environ Sci Technol; 16(3):131-136 1982

Inhalation exposure of workers was studied with personal air monitors and high-vol pumps mounted on tractors and placed in treated fields during and following application of the herbicide trifluralin containing 2-6 ppm N-nitrosodipropylamine (NDPA). No significant risk of exposure to NDPA was found under both simultaneous and sequential application-soil incorporation techniques. Currently produced trifluralin contains much less NDPA than that tested. The dipropylamine contaminant in the trifluralin was not converted to NDPA in the collection equipment. (20 Refs)

54. AN ASSESSMENT OF THE IMPLICATIONS OF NITRATE-RICH WATER ON SALIVARY NITRATE.

Weisenberg E, Grauer F, Baron Y, Rajstein J

Inst. Control and Standardisation of Drugs, P.O. Box 1457, Jerusalem 91013, Israel

Ecotoxicol Environ Saf; 6(1):97-101 1982

Two groups of 16 volunteers each ingested drinking water containing different amounts of nitrate (98 mg NO3-/liter, test group; 3.8 mg NO3-/liter, control group), and variations in salivary nitrate and nitrite concentration were determined for the next 2 hr. An increase in salivary nitrate and nitrite was observed in all subjects according to the amount of nitrate in the water. The increase was first noted shortly after water was ingested and peaked within approx 90 min. Large individual variations were found in the salivary nitrite. The differences between the two groups in nitrate and nitrite salivary content were not significant at zero time but reached significance at 1 and 2 hr after ingestion. Thus, an interplay exists between ingested nitrate and the concentration of salivary nitrite. The importance of further study of the kinetics of nitrate in humans and of factors related to the reduction of nitrate and nitrite in the oral cavity, including the role of accelerators or inhibitors in the process of nitrosable amino-nitrite interaction, is noted. (19 Refs)

55. NONDETECTION OF O(6)-METHYLGUANINE IN RAT DNA FOLLOWING IN VIVO TREATMENT WITH LARGE DOSES OF CIMETIDINE ALONE OR IN COMBINATION WITH SODIUM NITRITE.

Kyrtopoulos SA, Hadjiloucas E, Vrotsou B

Natl. Hellenic Res. Foundation, Biological Res. Center, 48 Vassileos Constantinou Ave., Athens, T.T. 501/1, Greece

Cancer Res; 42(5):1962-1966 1982

Cimetidine was administered by stomach tube to rats at 70 or 700 mg/kg, doses corresponding to 5 or 50 times, respectively, the typical daily dose of individuals on cimetidine treatment. In some cases, cimetidine (70 mg/kg) was administered in combination with a two-fold molar excess of sodium nitrite. This treatment was carried out up to six times over a 3-day period, the pH of the rat stomach being maintained at 2.3 to 3.0 for about 1 hr after each treatment. The DNA of the stomach, liver, and intestines (large and small pooled together) were isolated 6 hr after cessation of treatment and analyzed for the presence of O6-methylguanine using a sensitive and specific radioimmunoassay. No evidence could be obtained for the presence of this methylated base in any of the DNA samples examined, the limit of detection being 3 umol O6-methylguanine per mol guanine. We suggest that the observed lack of DNA methylation may be primarily due to the slow rate of nitrosation of cimetidine in combination with its rapid absorption into the blood stream. (Author abstract) (38 Refs)

56. OPPORTUNITIES AND CHALLENGES FOR COOPERATION BETWEEN THE UNITED STATES AND CHINA IN CANCER RESEARCH.

Handler P

Natl. Acad. Sciences, Washington, DC

Cancer Research in the People's Republic of China and the United States of America: Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. Marks PA, ed. New York, Grune and Stratton, 273 pp., 1981.

Areas of potential opportunities for cooperation between the United States and China in cancer research are proposed. Those areas are epidemiology, carcinogenesis, new drug development, and basic biological research. Studies of possible carcinogenic substances in the regional high-risk cancer areas have potential for collaborative ventures. The possible role of nitrosamines and their precursors in drinking water and foodstuffs of inhabitants of high-risk area in development esophageal cancer has been reported. New drug development focusing on plants that have been employed in traditional Chinese medicine is reviewed. (no Refs)

57. STUDIES ON POTENTIAL CARCINOGENS IN THE DIET OF INDIVIDUALS AT HIGH RISK FOR ESOPHAGEAL CANCER.

Li MH

Inst. Cancer Res., Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Cancer Research in the People's Republic of China and the United States of America: Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. Marks PA, ed. New York, Grune and Stratton, 273 pp., 1981.

Studies on etiological agents of esophageal cancer in the high-risk areas are discussed. Environmental factors apparently play an important role in the development of esophageal cancer. Some foodstuffs in Linxian are frequently contaminated by Fusarium moniliforme and other fungi. Formation of di-

ylnitrosamine, diethylnitrosamine, ylbenzylnitrosamine, and a new volatile N-nitroso compound, N-1-methylacetonyl-N-3-methylbutylnitrosamine has demonstrated in moldy cornbread after an 8-day incubation when a small amount of $NaNO_2$ was added initially. er contributing factors in the environment are nutritional ciencies in animal protein and fat, vitamins A, B2, and C, levels of nitrates and nitrites in water and food, low molenum and zinc, imbalance of trace elements, and indoor air ution from coal stoves during the winter. (10 Refs)

ASPECTS OF RESEARCH STUDIES ON LIVER RCINOMA.

hen Y
anghai Inst. Cell Biology, Academia Sinica, Shanghai, People's Republic of China
ancer Research in the People's Republic of China and the United States of America: Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. Marks PA, ed. New York, Grune and Stratton, 273 pp., 1981.

Studies with human liver carcinoma (HLC) and rat hepaa are summarized. In vitro cultured HLC cell lines, fetal igens in HLC, localization of surface and core antigen of patitis B virus in human hepatoma, cell-mediated cytotoxiy and immune RNA studies in human hepatoma, and experintal hepatoma research are discussed. A transplantable rat patoma was established by feeding Wistar rats with diethylrosamine in drinking water. The hepatoma exhibited fetal aracteristics, including alpha-fetoprotein production, fetal zyme expression, and the presence of membrane-associated al antigen. Research using these model systems and liver maial derived from animals during carcinogenesis and from renerated and fetal livers is described. (19 Refs)

. UNDERESTIMATED: NITROSAMINES IN SMOKE.

Remmer H
Institut fur Toxikologie der Universitat Tubingen, Wilhelmstrasse 56, D-7400 Tubingen, W. Germany
MMW; 124(4):12-13 1982

Importance of nitrosamines (NA), especially dimethylnitrosaine, in the cigarette smoke is discussed. Smokers and passive nokers are equally exposed to NA in the same working and creational areas. NA affect mostly lungs and liver causing ncer. (In GER)

. NO PROOF OF HEALTH HAZARD.

Schievelbein H
Institut fur Klinische Chemie, Deutsches Herzzentrum, Lothstr. 11, D-8000 Munchen 2, W. Germany
MMW; 124(4):13-15 1982

Health hazards of passive smoking (PS) are reviewed. PS resents an inconvenience for a healthy adult, but no evidence f a real hazard for health was yet presented. Forty carcinoenic components could be determined in cigarette smoke, maority of which are released into the ambient atmosphere and ould be inhaled by the passive smoker. Nitrosamines deserve pecial attention. (In GER)

1. CONCLUSION: EXTENT OF SPECULATION.

Lehnert G
Zentralinstitut fur Arbeitsmedizin, Adolph-Schonfelder-Str. 5, D-2000 Hamburg 76, W. Germany
MMW; 124(4):19-20 1982

Influence of passive smoking on health is reviewed. Air concentrations of dimethylnitrosamine (NDMA) and estimated NDMA concentrations in humans inhaled during 8 hr exposure to cigarette smoke are presented. According to presented data health hazards caused by inhalation of NDMA are speculative. (10 Refs) (In GER)

REVIEWS INCLUDING NITROSO COMPOUNDS

62. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN. SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.

Schmahl D
International Agency for Cancer Research, Lyon, France
IARC Mongr Eval Carcinog Risk Chem Hum 26: 411 pp., 1981.

The carcinogenic risk to humans of some antineoplastic and immunosuppressive agents is reviewed and analyzed and areas in which additional research is needed are discussed. The compounds considered, include alkylating agents, antimetabolites, mitotic inhibitors, and/or immunosuppressants. Alkylating agents are generally carcinogenic and mutagenic and produced tumors at multiple organ sites. For most drugs, only case reports were available for study. Whenever possible, concern about late complications was considered. Monographs are presented on 5-azacytidine, azathioprine, bischloroethyl nitrosourea, bleomycins, chlorambucil, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, cisplatin, cyclophosphamide, dacarbazine, 5-fluorouracil, isophosphamide, 6-mercaptopurine, methotrexate, prednisone, procarbazine hydrochloride, treosulphan, vinblastine sulfate, and vincristine sulfate. (1545 Refs)

63. BACTERIAL COLONIZATION FOLLOWING RESECTIVE AND NONRESECTIVE GASTRIC SURGERY.

Falter E, Preac-Mursic V, Hellerer O, Bruckner WL
Chirurgische Poliklinik, Universitat Munchen, Pettenkoferstr. 8a, D-8000 Munchen 2, W. Germany
Z Gastroenterol; 20(1):33-39 1982

Bacterial growth following resective and nonresective gastric surgery was studied in 120 male Sprague-Dawley rats. Groups of 20 rats each underwent laparotomy (control), selective proximal vagotomy (SPV) with preservation of the innervation of the antrum, SPV with pyloroplasty (SPV + Pypl), trunk vagotomy (TV) with pyloroplasty (TV + Pypl), antecolic resection according to Billroth II without enteroanastomosis (BII), or BII + TV. At 8 mo after surgery smears were obtained under general anesthesia from the transitional segment between the fundus and the antrum or from the site of anastomosis. Smears were examined for aerobic and anaerobic bacteria and fungi. Control rats and those that underwent SPV + Pypl showed similar total bacterial counts and relative nitrobacter fractions. Rats that underwent SPV, BII, or BII + TV had nitrobacter counts approx 10x as high as those in control rats. Rats that underwent BII + TV had total bacteria counts approx 3x as high as those in rats that underwent BII without TV. Comparison of the test groups indicates that bacterial growth in the stomach was promoted by reduced production of gastric acid, reflux of bile secretions, and retarded food passage. Increased bacterial growth promoted intragastric formation of carcinogenic nitrosamines. (28 Refs) (In GER)

64. NUMBER OF SPECIES AND TAXONOMY OF ANIMALS IN WHICH N-NITROSO COMPOUNDS ARE CARCINOGENIC.

Bogovskii SP, Bogovskii PA
Inst. Experimental and Clinical Medicine, Tallin, USSR
Eksp Onkol; 4(1):60-63 1982

Carcinogenic effects of eight nitroso compounds (NC) in different animal species are reviewed. NC were found to induce tumors in 39 animal species from 36 genders, 25 families, 17 orders, and 5 classes. These findings indicate the high probability that NC are also carcinogenic for humans. (22 Refs) (In RUS)

☆ U.S. GOVERNMENT PRINTING OFFICE: 1982—361-847/123

AUTHOR INDEX WITH CITATION NUMBERS

Abbondandolo A. 41
Althoff J. 15
Althoff J. 4
Althoff J. 6
Amacher DE. 25
Arlett CF. 49
Autrup H. 1
Barnhart BJ. 33
Baron Y. 54
Berends F. 41
Bogovskii PA. 64
Bogovskii SP. 64
Boyle JM. 42
Bruckner WL. 63
Bykorez AI. 17
Chastain B. 10
Chen DJ. 33
Cherni S. 20
Cherry LM. 34
Clatterbuck BE. 45
Cleaver JE. 39
Cohadon F. 8
Cole J. 49
Cole RJ. 49
Coulston F. 52
Day EW. 53
Deen DF. 35
Deen DF. 48
DiPaolo JA. 37
Dogliotti E. 41
Dolezhalova V. 20
Durrant LG. 42
Epstein SM. 37
Evans FE. 2
Falter E. 63
Fiebig HH. 13
Frank R. 53
Furukawa K. 43
Furuta K. 5
Gilbert PJ. 23
Gorban' GP. 20
Gotoh M. 43
Grauer F. 54
Green U. 15
Green U. 4
Griggs RD. 53
Grinchishin VP. 17
Hadjiloucas E. 55
Hallstrom I. 30
Hanaoka F. 38
Handler P. 56
Hauenstein KH. 13
Hayward IP. 44
Heidelberger C. 32
Helgeson S. 14
Hellerer O. 63
Henderson L. 49
Hines L. 14
Hodges GM. 16
Holland JM. 10
Hsie AW. 27
Hsu TC. 34
Iannaccone PM. 47
Isobe M. 24
Ito A. 7
Ito H. 22
Jones M. 31
Kadlubar FF. 2
Kamiya S. 5
Kammermeyer KL. 29
Kato H. 38
Kauffmann G. 13
Ketkar MB. 6
Ketterer B. 2
Koestner A. 50
Kosako Y. 22
Kraus W. 13
Krause-Leiphold. 11
Krieg L. 11
Kyrtopoulos SA. 55
Lawson T. 14
Lehnert G. 61
Li MH. 57
Lijinsky W. 6
Liu H. 18
Lohman PH. 41
Machanoff R. 27
Maekawa A. 5
Magee PN. 51
Magnusson J. 30
Marton LJ. 48
Matsuoka C. 5
McKinney EM. 53
Medline A. 21
Mercier M. 23
Meyer SA. 45
Mironescu SG. 37
Mochizuki Y. 43
Montgomery CS. 26
Morrison LE. 44
Moshell AN. 45
Mosler JW. 53
Mudrak I. 40
Mulder GJ. 2
Mulkins MA. 32
Naito M. 7
Naito Y. 7
Nathrath WJ. 16
O'Neill JP. 27
Ogawa K. 19
Ohta A. 12
Okinaka RT. 33
Olajos EJ. 52
Onodera H. 5
Onoe T. 19
Oredsson SM. 48
Oshima M. 12
Park SD. 39
Parsons PG. 44
Pathak S. 34
Peterson AR. 28
Peterson H. 28
Pliss MB. 20
Poncelet F. 23
Pour P. 14
Pour PM. 3
Powers FL. 53
Preac-Mursic V. 63
Rajstein J. 54
Ramel C. 30
Remmer H. 59
Robbins JH. 45
Rollmann B. 23
Rondelet J. 23
Rosen JM. 9
Rubenchik BL. 20
Russell LB. 26
Ryuzaki M. 12
Salmasi SZ. 3
San Sebastian J. 27
Saunders DG. 53
Sawada N. 43
Scarpinato RG. 45
Schievelbein H. 60
Schmahl D. 62
Schneider P. 15
Scudiero DA. 45
Shapiro JR. 36
Shapiro WR. 36
Shimamoto F. 22
Shugart L. 10
Simickova M. 20
Smellie SG. 44
Soudah B. 15
Stols L. 47
Stoner GD. 1
Stratil P. 20
Strecker EP. 13
Strniste GF. 33
Sumiyoshi H. 22
Summerhayes IC. 16
Supowit SC. 9
Tahara E. 22
Taniyama K. 22
Tarone RE. 45
Taylor N. 49
Tomoyori T. 19
Trejdosiewicz L. 16
Tsao TY. 47
Tsukada H. 43
Turner GN. 25
Unruh LE. 2
Villani G. 46
Vinarchuk MP. 17
Vinores SA. 50
Volm M. 11
Vrotsou B. 55
Wagner R. 31
Wang F. 18
Wang Z. 18
Wanless IR. 21
Wayss K. 11
Weinkam RJ. 35
Weisenberg E. 54
Wilson PD. 16
Wintersberger E. 40
Yamada K. 38
Yamada M. 38

Yano K..... 24
Yokokawa K..... 19
Yung WK..... 36
Zhang Z..... 18
Zhen Y..... 58
Zimmering S..... 29

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN. SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.
Schmahl D
International Agency for Cancer Research, Lyon, France
IARC Mongr Eval Carcinog Risk Chem Hum 26: 411 pp., 1981.

2. BIOCHEMICAL TOXICOLOGY OF BENZENE.
Snyder R, Longacre SL, Witmer CM, Kocsis JJ, Andrews LS, Lee EW
Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, PA, 19107
Rev Biochem Toxicol; 3:123-153 1981

3. A REVIEW OF THE MUTAGENICITY OF CHROMIUM.
Hatherill JR
Toxicology, Sch. Public Health, Univ. Michigan, Ann Arbor, MI, 48109
Drug Chem Toxicol; 4(3):185-195 1981

4. HORMONES AND BREAST CANCER.
Pike MC, Siiteri PK, Welsch CW
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Banbury Rep 8: 491 pp., 1981.

5. ORAL CONTRACEPTIVES: VOLUME 5.
Briggs MH, Briggs M
Deakin Univ., Geelong 3217, Australia
Oral Contraceptives: Volume 5. St. Albans, VT, Eden Medical Research Inc., Annual Research Reviews--Endocrinology, 331 pp., 1981.

6. EPIDEMIOLOGICAL STUDIES OF THE ROLE OF EXOGENOUS ESTROGENS IN THE ETIOLOGY OF BREAST CANCER.
Kelsey JL, Bulbrook RD, Korenman SG, Siiteri PK, Henderson BE
Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Banbury Rep; 8:215-228 1981

7. EFFECTS OF LONG-TERM EXPOSURE TO LOW LEVELS OF OZONE. A REVIEW.
Melton CE
Civil Aeromedical Inst., Federal Aviation Admin., Oklahoma City, OK, 73125
Aviat Space Environ Med; 53(2):105-111 1982

8. METABOLIC INTERACTIONS OF HYDROCARBONS WITH MAMMALIAN LUNG.
Smith BR, Bend JR
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Rev Biochem Toxicol; 3:77-122 1981

9. REVIEW OF EXPERIMENTAL CARCINOGENESIS BY COMPOUNDS RELATED TO VINYL CHLORIDE.
Chu KC, Milman HA
NCI, Bethesda, MD, 20205
Environ Health Perspect; 41:211-220 1981

10. REVIEWS IN BIOCHEMICAL TOXICOLOGY.
Hodgson E, Bend JR, Philpot RM
North Carolina State Univ., Raleigh, NC
Rev Biochem Toxicol 3: 368 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

11. ALCOHOL AND CANCER.
MacSween RN
Univ. Dept. Pathology, Western Infirmary, Glasgow, Scotland
Br Med Bull; 38(1):31-33 1982

12. THE TOXICOLOGY OF COCOA AND METHYLXANTHINES: A REVIEW OF THE LITERATURE.
Tarka SM
Life Sciences, Hershey Foods Corp., Corporate Technical Center, Hershey, PA
CRC Crit Rev Toxicol; 9(4):275-312 1982

13. IMPLICATIONS OF DIETARY FIBER BREAKDOWN IN THE HUMAN COLON.
Cummings JH, Stephen AM, Branch WJ
MRC Dunn Clinical Nutrition Centre, Old Addenbrookes Hosp., Cambridge, CB2 1QE, England
Banbury Rep; 7:71-81 1981

14. BILE SALTS AND OTHER CONSTITUENTS OF THE COLON AS TUMOR PROMOTERS.
Reddy BS, Tannenbaum SR, Montesano R, Correa P, Haenszel W, Wattenberg LW
Div. Nutrition, American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY, 10595
Banbury Rep; 7:345-363 1981

15. MOLD PRODUCING CARCINOGENIC TOXINS IN FOOD PRODUCTS.
Preda N
Institutul de medicina si farmacie, Cluj-Napoca, Romania
Rev Chir [Oncol]; 20(1):1-9 1981
In RUM

16. THE MEANING OF CANCER 'DIETS'.
Jungi WF
Abt. f. Onkologie-Hamatologie, Medizinische Klinik C, CH-9007 St. Gallen, Switzerland
MMW; 124(2):26-28 1982
In GER

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

17. RISK FACTORS FOR CERVICAL CANCER.
Hulka BS
Dept. Epidemiology, Rosenau Hall 201H, Univ. North Carolina, Chapel Hill, North Carolina, NC, 27514
J Chronic Dis; 35(1):3-11 1982

18. EPIDEMIOLOGY OF THE MOST FREQUENTLY OCCURRING TUMORS OF THE DIGESTIVE SYSTEM.
Naujoks-Heinrich S, Dolle W
Abteilung Innere Medizin I, Universitatsklinik, Otfried-Muller-Strasse 10, D-7400 Tubingen, W. Germany
Internist (Berlin); 23(1):1-9 1982
In GER

19. BLADDER CANCER.
Skrabanek P, Walsh A
Endocrine Oncology Unit, Mater Misericordiae Hosp., Dublin, Ireland
UICC Tech Rep Ser 60: 192 pp., 1981.

20. RECENT ADVANCES IN CANCER CYTOGENETICS.
Pogosiants EE
All-Union Cancer Res. Center, Moscow, USSR
Genetika; 17(12):2087-2099 1981
In RUS

21. CURRENT STATUS OF CYTOGENETIC STUDIES IN ANIMAL TUMORS WITH SPECIAL REFERENCE TO NONRANDOM CHROMOSOME CHANGES.
Sasaki M
Chromosome Res. Unit, Hokkaido Univ., Faculty Science, Sapporo 060, Japan
Cancer Genet Cytogenet; 5(2):153-172 1982

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

22. ASBESTOS-RELATED DISEASES.
Casey KR, Rom WN, Moatamed F
Building 512, RMCOEH, Univ. Utah Medical Center, Salt Lake City, UT, 84112
Clin Chest Med; 2(2):179-202 1981

23. NONASBESTOS FIBROUS MINERALS.
Lockey JE
Building 512, RMCOEH, Univ. Utah Medical Center, Salt Lake City, UT, 84112
Clin Chest Med; 2(2):203-218 1981

24. REVIEW OF EPIDEMIOLOGIC STUDY RESULTS OF VINYL CHLORIDE-RELATED COMPOUNDS.
Apfeldorf R, Infante PF
Office Carcinogen Identification and Classification, Health Standards, Programs, Occupational Safety and Health Admin. U. S. Dept. Labor, Washington, DC, 20210
Environ Health Perspect; 41:221-226 1981

25. CONCEPTS IN CAUSALITY: CHEMICALLY INDUCED HUMAN URINARY BLADDER CANCER.
Lower GM
Center Human Systems, Inst. Environmental Studies, Univ. Wisconsin, WARF Building, 610 Walnut St., Madison, WI, 53706
Cancer; 49(5):1056-1066 1982

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

26. MOLECULAR MECHANISM OF ADAPTATION OF CELLS TO LOW LEVELS OF CARCINOGENIC AGENTS.
Villani G
Laboratoire de Pharmacologie et de Toxicologie Fondamentales, CNRS, 205, route de Narbonne, 31078 Toulouse Cedex, France
Pathol Biol (Paris); 30(2):117-123 1982
In FRE

27. MIGHT CANCER BE A FAILED RESPONSE TO RENEGADE MITOCHONDRIA?
Hartung J
Dept. Anesthesiology, State Univ. New York, Downstate Medical Center, Brooklyn, NY, 11203
J Theor Biol; 94(1):173-178 1982

MODIFICATION OF CARCINOGENESIS

28. EFFECT OF GEROPROTECTORS ON CARCINOGENESIS.
Anisimov VN
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Usp Sovrem Biol; 92(3):455-472 1981
In RUS

29. RELATION OF NEUROLEPTIC DRUGS TO DEVELOPMENT AND GROWTH OF MAMMARY TUMORS.
Meites J, Aylsworth CF
Dept. Physiology, Neuroendocrine Res. Lab., Michigan State Univ., East Lansing, MI, 48824
Banbury Rep; 8:365-376 1981

30. THE ACTIONS OF INSULIN AS A HORMONAL FACTOR IN BREAST CANCER.
Hilf R, Siiteri PK, Shellabarger, Korenman SG, Rosen, Nandi
Dept. Biochemistry and Univ. Rochester Cancer Center, Univ. Rochester, Rochester, NY, 14642
Banbury Rep; 8:317-337 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

31. ONCOGENES.
Bishop JM
Univ. California, San Francisco, CA
Sci Am; 246(3):80-84,87-92,154 1982

32. HUMAN CANCERS AND HUMAN VIRUSES.
Waterson AP
Royal Postgraduate Medical Sch., London W12 0HS, England
Br Med J; 284(6314):446-448 1982

33. THE IMMUNOLOGY OF CANCER OF THE HEAD AND NECK WITH PARTICULAR REFERENCE TO ORAL CANCER.
Scully C
Univ. Dept. Oral Medicine and Pathology, Immunology Unit, Glasgow Dental Hosp., 378 Sauchiehall St., Glasgow G2 3JZ, Scotland
Oral Surg; 53(2):157-169 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

34. THE USE OF MAMMALIAN CELL MUTANTS TO STUDY THE MECHANISMS OF CARCINOGENESIS.
Trosko JE, Chang CC, Warren ST, Liu PK, Wade MH, Tsushimoto G
Dept. Pediatrics and Human Development, Michigan State Univ., Coll. Human Medicine, East Lansing, MI, 48824
Gann Monogr Cancer Res; 27:159-179 1982

35. BIOLOGICAL MONITORING IN THE IDENTIFICATION OF THE CANCER RISK OF INDIVIDUALS EXPOSED TO CHEMICAL CARCINOGENS.
Vainio H, Sorsa M, Rantanen J, Hemminki K, Aitio A
Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 7(4):241-251 1981

36. A CRITICAL REVIEW OF BIOLOGICAL METHODS FOR THE DETECTION OF FUNGAL TOXINS IN FOODS AND FOODSTUFFS.
Watson DH, Lindsay DG
Food Science Div., Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, London SW1P 2AE, England
J Sci Food Agric; 33(1):59-67 1982

37. PITUITARY AND STEROID HORMONES IN RADIATION-INDUCED MAMMARY TUMORS.
Shellabarge: CJ
Medical Dept., Brookhaven National Lab., Upton, NY, 11973
Banbury Rep; 8:339-351 1981

38. ASPERGILLUS NIDULANS: SYSTEMS AND RESULTS OF TESTS FOR CHEMICAL INDUCTION OF MITOTIC SEGREGATION AND MUTATION. I. DIPLOID AND DUPLICATION ASSAY SYSTEMS. A REPORT OF THE U. S. EPA GENE-TOX PROGRAM.
Kafer E, Scott BR, Dorn GL, Stafford R
Dept. Biology, McGill Univ., 1205 Ave. Docteur Penfield, Montreal H3A 1B1, Canad a
Mutat Res; 98(1):1-48 1982

OTHER REVIEWS IN CARCINOGENESIS

39. MATHEMATICAL MODELS OF THE CELL CYCLE WITH A VIEW TO TUMOR STUDIES.
Bertuzzi A, Gandolfi A, Giovenco MA
Centro di Studio dei Sistemi di Controllo e Calcolo Automatici del C.N.R., Via Eudossiana 18, 00184 Rome, Italy
Math Biosci; 53(3/4):159-188 1981

40. NEOPLASMS IN DOMESTIC ANIMALS: A REVIEW OF EXPERIMENTAL AND SPONTANEOUS CARCINOGENESIS.

Madewell BR

Section Clinical Oncology, Dept. Veterinary Surgery, Univ. California, Davis, CA, 95616

Yale J Biol Med; 54(2):111-125 1981

VIDEOTAPES

ON CURRENT TOPICS IN CANCER RESEARCH

A pilot project of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute

Three series are available . . .

THE RELATION OF CARCINOGEN ACTION ON DNA TO CELL TRANSFORMATION

PETER MAGEE Fels Research Institute	*Keynote Address*	#VK01 28 min.
JAMES K. SELKIRK Oak Ridge National Laboratories	*Metabolic Activation and Macromolecular Binding of Chemical Carcinogens*	#VK02 51 min.
PHILIP C. HANAWALT Stanford University	*Cellular Responses to Damaged DNA*	#VK03 54 min.
CHARLES HEIDELBERGER University of Southern California	*Mutagenesis and Oncogenic Transformation of Mouse Embryo Cells*	#VK04 54 min.
FRED RAPP Milton S. Hershey Medical Center	*The Interaction of Herpesviruses and Host Cells Leading to Latency or Transformation*	#VK05 52 min.
	Panel Discussion	#VK06 31 min.

MECHANISMS OF METASTASIS

ISAIAH FIDLER Frederick Cancer Research Center	*The Heterogeneous Nature of Cancer Metastasis and Implications for Therapy*	#VB01 47 min.
GEORGE POSTE Smith, Kline and French Laboratories	*Phenotypic Analysis of Metastatic Cell Populations*	#VB02 42 min.
LANCE LIOTTA National Cancer Institute	*Tumor Cell Invasion of Basement Membranes and Extracellular Matrices*	#VB03 33 min.
EVERETT SUGARBAKER Miami Cancer Institute	*Some Clinical Characteristics of Metastasis in Man*	#VB04 41 min.

AUTOMATED CYTOLOGY

Part One: Principles and Techniques	#VB05 56 min.
Part Two: Biological Applications	#VB06 52 min.

VIDEOTAPES ON CURRENT TOPICS IN CANCER RESEARCH are in the 3/4" U-matic format and can be played on video equipment which accepts the NTSC standard (the standard for videotapes produced in the U.S.). The two Automated Cytology tapes (#VB05 and #VB06) are also available in the PAL format.

The videotapes are available on a loan basis. If you would like to schedule viewing for your group, or for more information, please write to:

Videotape Coordinator
ICRDB Program
Westwood Building, Room 10A18
Bethesda, MD 20205

Please specify three choices for viewing dates, and the tapes desired.

CANCER INFORMATION? CANCERLINE·CANCERLINE·CANCERLINE·

Keep Up with the Cancer Literature

Each Month
You Can Receive Abstracts
Covering Your Specialty Area

- This convenient service — called Auto SDI* — is as near as your nearest biomedical library. Discuss your research interests with the librarian who will design an appropriate search strategy.
- Abstracts of the latest published literature are searched automatically each month and those related to your interests are delivered to you on a regular basis.
- The abstracts you receive are selected from more than 4,000 monthly entries made into CANCERLIT — the extensive cancer literature data base of the National Cancer Institute.

Talk With Your Librarian
About the Auto SDI Service TODAY.

*Auto SDI stands for Automatic Selective Dissemination of Information. It is a service provided to you, at minimal cost, by the International Cancer Research Data Bank (ICRDB) — a part of the National Cancer Institute.

CANCERGRAMS are distributed for the International Cancer Research Data Bank (ICRDB) by the National Technical Information Service (NTIS). **CANCERGRAMS** are available from NTIS on a standing order basis at $2 each for North American Continent addressees and $3 each for other addressees. An NTIS deposit account is required. For a list of subject categories or other information, please write to:

Subscription Section
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
5285 Port Royal Road
Springfield,Va 22161

OFFICIAL BUSINESS

Penalty for Private Use, $300

PRINTED MATTER

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF COMMERCE
COM-211

THIRD CLASS
BULK RATE

CK-01

NOTICE OF MAILING CHANGE

☐ Check here if you wish to discontinue receiving this publication.

☐ Check here if your address has changed and you wish to continue receiving this publication. (Be sure to furnish your complete address including zip code.)

Tear off cover with address label still affixed and send to:

Computer Support Center
ICRDB Program
IIT Research Institute
10 West 35th Street
Chicago IL. 60616

CK 01/82/09

NCI/ICRDB/CK01 82/09

PB82-935109

ICRDB CANCERGRAM

CHEMICAL CARCINOGENESIS

Nitroso Compounds

SERIES CK01 No. 82/09

SEPTEMBER, 1982

This Cancergram is a service of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM of the U.S. National Cancer Institute. Every few weeks, an updated Cancergram containing abstracts of selected cancer-related articles recently published in more than 3000 journals, and dealing with the topic indicated by the above title, is sent to researchers working in this area. These researchers are identified on the basis of the description of their current research project that has been submitted to the ICRDB Program, directly or via granting agencies.

This Cancergram is prepared by the Cancer Information Dissemination and Analysis Center (CIDAC) for Carcinogenesis Information. ***If this Cancergram is useful and valuable, please send your comments to the CIDAC address below, since future editions depend on user satisfaction and user needs:***

CIDAC FOR CARCINOGENESIS INFORMATION
SCIENCE INFORMATION SERVICES
FRANKLIN INSTITUTE RESEARCH LABORATORIES
20TH AND RACE STREETS
PHILADELPHIA, PA 19103

NEWARK PUBLIC LIBRARY

SEP 30 1982

U. S. GOVT. PUBS.
DEPOSITORY 376

PDQ (PROTOCOL DATA QUERY) - A NEW ONLINE CANCER DATABASE WILL BE AVAILABLE THIS FALL! PDQ LISTS THERAPY PROTOCOLS PLUS ADDRESSES AND PHONE NUMBERS OF CLINICAL INVESTIGATORS. CONTACT ICRDB FOR DETAILS.

In this issue:

- FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS 1-2
- METABOLISM OF NITROSO COMPOUNDS 3-9
- INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS 10-24
- MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS 25-33
- MUTAGENICITY OF NITROSO COMPOUNDS 34-45
- CELLULAR EFFECTS OF NITROSO COMPOUNDS 46-53
- IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS 54-56
- EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS 57-59

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20.3173/2:

FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS

1. IN VIVO STABILITY OF NITRITE AND NITROSAMINE FORMATION IN THE DOG STOMACH: EFFECT OF NITRITE AND AMINE CONCENTRATION AND OF ASCORBIC ACID.

Lintas C, Clark A, Fox J, Tannenbaum SR, Newberne PM
Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Carcinogenesis; 3(2):161-165 1982

Formation of N-nitrosodimethylamine (NDMA) from the precursors nitrite and dimethylamine has been studied in the chronically fistulated dog stomach. Measurements have also been made as a function of time for nitrite stability and gastric pH, and a nonabsorbable marker has been used to correct for gastric emptying and dilution. In the fasting animal NDMA forms within minutes after addition of the reactants if the pH is below 5. The presence of food in the stomach slows the reaction, and the additional presence of ascorbic acid greatly depresses the amount of NDMA formed. The concentration of nitrite in gastric juice declines rapidly after its introduction, but the concentration of NDMA declines even more rapidly than nitrite. This suggests that NDMA is probably rapidly absorbed directly from the dog stomach, in contrast to earlier results in rodent experiments. (Author abstract) (16 Refs)

2. NEW STEROIDAL NITROSOUREAS.

Chavis C, De Gourcy C, Borgna JL, Imbach JL
Laboratoire de Chimie Bio-Organique, Equipe de Recherche Associee n 195 du, CNRS Universite des Sciences et Techniques du Languedoc, Place E.Bataillon, 34090 Montpellier, France
Steroids; 39(2):129-147 1982

Seventeen beta and 20 nitrosourea derivatives belonging to the dehydroepiandrosterone, estrone and pregnenolone series have been synthesized. The behavior of these compounds towards the calf uterine estradiol and pregnenolone receptors have been studied. (Author abstract) (29 Refs)

METABOLISM OF NITROSO COMPOUNDS

3. RELATIONSHIP BETWEEN CARCINOGENICITY AND IN VITRO METABOLISM OF NITROSOMETHYLETHYLAMINE, NITROSOMETHYL-N-BUTYLAMINE, AND NITROSOMETHYL(2-PHENYLETHYL)AMINE LABELED WITH DEUTERIUM IN THE METHYL AND ALPHA-METHYLENE POSITIONS.

Farrelly JG, Stewart ML, Saavedra JE, Lijinsky W
Chemical Carcinogenesis Program, NCI-Frederick Cancer Res. Facility, Frederick, MD, 21701
Cancer Res; 42(6):2105-2109 1982

With the use of rat liver preparations, the in vitro microsomal metabolism of methylethylnitrosamine, methyl-n-butylnitrosamine, and methyl(2-phenylethyl)nitrosamine labeled with deuterium in the methyl and alpha-methylene positions has been compared with that of the parent (unlabeled) compounds. All three forms of the liver carcinogen methylethylnitrosamine are metabolized with two sets of kinetic constants. Examination of these kinetic constants suggests that both methylation and ethylation of cellular nucleophiles might be important in the carcinogenic action of these nitrosamines. The esophageal carcinogen, methyl(2-phenylethyl)nitrosamine, gave only one set of kinetic constants during metabolism. The metabolism of the three methylbutylnitrosamines gave results similar to that of the three methylethyl nitrosamines. Except for metabolism of d2-methylbutylnitrosamine to butyraldehyde, two sets of kinetic constants were found. Approximately equivalent amounts of methylating species were produced from d3-methylbutylnitrosamine and d0-methylbutylnitrosamine. (Author abstract) (16 Refs)

4. FLUORO-SUBSTITUTED N-NITROSAMINES. 2. METABOLISM OF N-NITROSODIETHYLAMINE AND OF FLUORINATED ANALOGS IN LIVER MICROSOMAL FRACTIONS.

Janzowski C, Pool BL, Preussmann R, Eisenbrand G
Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Carcinogenesis; 3(2):155-159 1982

In vitro metabolism of N-nitrosodiethylamine (NDEA) and of its two fluorinated analogs N-nitroso-2,2,2-trifluoroethylethylamine (NDEA-F3) and N-nitroso-bis(2,2,2-trifluoroethyl)amine (NDEA-F6) was comparatively investigated using rat liver microsomes and S-9 fraction. Aldehydes, nitrite and unchanged nitrosamines were determined. Additionally the mutagenicity was measured in a Salmonella/mammalian microsome assay. NDEA and NDEA-F3 were deethylated and, to a smaller extent, denitrosated. Dealkylation of NDEA-F3 at the fluorinated ethyl group, however, was strongly inhibited. NDEA-F6 was practically not metabolized under the in vitro conditions used. In contrast to NDEA, the mutagenicity of NDEA-F3 was at best marginal; NDEA-F6 was not mutagenic. The results show that substitution of fluorine in beta-position of NDEA strongly influences alpha-C-hydroxylation and denitrosation. (Author abstract) (20 Refs)

5. DIMETHYLNITROSAMINE ADDUCTS EXCRETED IN RAT URINE.

Hemminki K
Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Chem Biol Interact; 39(2):139-148 1982

Rats were injected with [14C]dimethylnitrosamine and urine was collected up to 5 days after the injection. Urine samples were concentrated and subjected to Sephadex G-10 chromatography. Three peaks of radioactivity (I-III, in the order of elution) were observed for all injection times. The peaks were analyzed further by cation exchange and thin-layer chromatography and by phase-separation (pH-determination). The pK-determinations and the chromatographic properties suggested that Sephadex fraction I is composed of methylated amino acids, such as N-acetyl-S-methylcysteine, 1-methylhistamine and S-methylcysteine, in addition to radioactive methionine. Sephadex fraction II was composed of allantoin and of a metabolite of thiazolidine-4-carboxylic acid. The latter compound was a reaction product of formaldehyde and cysteine, indicating activity of the formaldehyde moiety released from dimethylnitrosamine. By gel filtration properties Sephadex fraction III indicated identity as 7-methylguanine. Altogether the urinary radioactivity accounted for about 9% of the applied dose. (Author abstract) (27 Refs)

6. ABSORPTION OF N-NITROSO-BIS-(2-HYDROXY-PROPYL)AMINE (BHP) FROM SUBCUTANEOUS LAYERS.

Bertram B, Schaffer R
Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
J Cancer Res Clin Oncol; 103(1):105-106 1982

Nodules developing under the skin of rats after repeated injections of N-Nitroso-bis-(2-hydroxy-propyl)amine (BHP) are shown to contain no unchanged BHP. (Author abstract) (7 Refs)

7. METABOLIC ACTIVATION OF DIMETHYLNITROSAMINE TO MUTAGENS: ROLE OF CYTOCHROMES P-450 AND P-448.

Phillipson CE, Ioannides C, Parke DV
Biochemistry Dept., Univ. Surrey, Guildford, Surrey, GU2 5XH, England
Toxicol Lett; 11(1/2):95-101 1982

Activation of dimethylnitrosamine (DMN) by hamster liver mixed function oxidase enzymes after pretreatment with various inducing agents was investigated. Induction of liver microsomal enzymes in male hamsters was achieved by ip administration of phenobarbitone (PBT: 80 mg/kg body wt), 3-methylcholanthrene (MCA: 20 mg/kg), or Aroclor 1254 (A-1254: 500 mg/kg) for 3 days. Ethoxyresorufin O-deethylase (EOD), NADPH-cytochrome c reductase, and cytochrome P-450 activities were assayed in liver microsomal suspension by the Ames test. Cytochrome P-450 concentrations increased to 1.29, 1.53, and 2.16 nanomole/mg protein after induction with PBT, MCA, and A-1254, respectively, compared to control levels of 0.61 nanomole/mg protein. EOD levels increased to 1.99 and 0.72 nanomole/min/mg protein after induction with MCA and A-1254, respectively, compared to control levels of 0.32 nanomole/min/mg protein. EOD levels were unaffected by PBT. NADPH-cytochrome c reductase levels increased to 63 and 80 nanomole/min/mg protein after induction with PBT and A-1254, respectively, compared to control level of 44 nanomole/min/mg protein. Cytochrome c reductase was unaffected by MCA. Pretreatment with PBT, MCA, or A-1254 did not significantly alter the capacity of liver microsomes to activate DMN to mutagens. Dimethylnitrosamine demethylase is either not involved in the metabolic activation of DMN, or is not the rate limiting step. (21 Refs)

8. METABOLIC NITRITE FORMATION FROM N-NITROSAMINES: EVIDENCE FOR A CYTOCHROME P-450 DEPENDENT REACTION.

Appel KE, Graf H
Section Toxicology, Inst. Pharmacology, Obere Zahlbacher Str. 67, D-6500 Mainz, W. Germany
Carcinogenesis; 3(3):293-296 1982

Nitrite was formed on incubation of N-nitrosamines with a reconstituted monooxygenase system, consisting of cytochrome P-450 (P-450) and NADPH P-450 reductase from pig liver. Nitrite was not obtained when the nitrosamines were incubated with NADPH P-450 reductase alone or when molecular oxygen or NADPH were omitted. Interaction of nitrosamines with the reconstituted P-450 system or with hemoglobin under reducing conditions resulted in optical spectra identical with those obtained with nitrite. It is proposed that N-nitrosamines are denitrosated by electron transfer from the hemoprotein iron to the nitrosamine molecule. (Author abstract) (27 Refs)

9. THE INDUCTION OF CYTOCHROME P-448 DEPENDENT BENZO(A)PYRENE HYDROXYLASE IN SACCHAROMYCES CEREVISIAE.

King DJ, Azari MR, Wiseman A
Bichemistry Div., Univ. Surrey, Guildford, Surrey, England
Biochem Biophys Res Commun; 105(3):1115-1121 1982

A form of cytochrome P450 with maximal absorption at 448 nanometers was induced in Saccharomyces cerevisiae grown in high glucose medium by benzo(a)pyrene (BP). The inability of BP to induce cytochrome P-448 in yeast grown in low glucose medium indicated that conditions similar to high glucose concentration may be required for cytochrome P-448 production. BP metabolism in yeast was also induced by dimethylnitrosamine and phenobarbital. 3-Methylcholanthrene induced a form of the enzyme with a higher affinity for BP. Addition of lanosterol to medium resulted in decreased affinity for BP. (18 Refs)

INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS

10. THE CARCINOGENICITY OF N-NITROSO COMPOUNDS: A SIMCA PATTERN RECOGNITION STUDY.

Dunn WJ, Wold S
Dept. Medicinal Chemistry, Coll. Pharmacy, Univ. Illinois Medical Center, 833 S. Wood, Chicago, IL, 60612
Bioorg Chem; 10(1):29-45 1981

The SIMCA method of pattern recognition was used to estimate the carcinogenic potential (CP) of a number of N-nitroso compounds in the rat. With the SIMCA method, classification as a carcinogen or non-carcinogen is based on physicochemical descriptions (data) of the compound, with the mathematical regularity within the data for each class represented by a principal components model. Data were obtained from published animal studies in which nitrosamines, N-nitroso ureas, and N-nitroso urethans had been tested. The nitroso compounds were administered to rats either in drinking water or by gavage. CP was evaluated coincident with location of tumor induction. Comparison of known CP data with SIMCA results showed that 88% of active compounds were correctly classified. This method, while theoretically based, gives an estimate of CP similar to that in the Ames mutagenicity test. (18 Refs)

11. ESOPHAGEAL CARCINOGENESIS IN F344 RATS BY NITROSOMETHYLETHYLAMINES SUBSTITUTED IN THE ETHYL GROUP.

Lijinsky W, Saavedra JE, Reuber MD, Singer SS
Chemical Carcinogenesis Program, NCI-Frederick Cancer Res. Facility, P.O. Box B, Frederick, MD, 21701
JNCI; 68(4):681-684 1982

The carcinogenic activity in male F344 rats of five nitrosomethylalkylamines related to nitrosomethylethylamine has been examined. All rats were tested by administration of controlled doses of the compounds in the drinking water. Nitrosomethylbenzylamine was the most potent carcinogen of the five, causing death of most animals with tumors of the upper gastrointestinal tract (mainly the esophagus) within 6 mo after a total dose of 0.2 mmol. The remaining compounds, all of which can be considered true derivatives of nitrosomethylethylamine, were less potent than

nitrosomethylbenzylamine but also induced a high incidence of tumors of the esophagus. Nitrosomethyl-2-phenylethylamine and nitrosomethylneopentylamine were of comparable potency, while nitrosomethyltrifluoroethylamine was considerably less potent, as measured by the time to death with esophageal tumors. Deuterium-labeled nitrosomethylethylamine, in which deuterium replaces hydrogen on the beta-carbon atom of nitrosomethylethylamine, induced a high incidence of esophageal tumors as well as liver tumors after administration of identical doses. Reactions on the beta-carbon atom of nitrosomethylethylamine might be important as well as oxidation at the alpha-carbon atoms in determining carcinogenic effects. (Author abstract) (16 Refs)

12. OBSERVATIONS ON INDUCED CARCINOSIS PERITONEI OF THE GUINEA PIGS.

van de Molengraft F, Jap P, Wirtz P, Vooijs P
(c/o Jap) Dept. Cytology and Histology, Univ. Nijmegen, Geert Grotteplein Noord 21, NL-6500 HB Nijmegen, The Netherlands
Virchows Arch [Cell Pathol]; 39(1):87-99 1982

A diethylnitrosamine-induced hepatocellular carcinoma cell suspension (line-10), injected intraperitoneally in Sewall Wright Strain-2 guinea pigs, causes ascites with implantation of malignant cells on the peritoneal surface. At these sites, swelling of the mesothelial cells and simultaneous proliferation of underlying fibroblasts and capillaries are seen. When there are about four layers of malignant cells and the mesothelial lining is disrupted, papillary projections of fibroblasts with capillaries, covered by malignant cells develop. These begin to behave as a 'tissue'. In these areas basement membrane destruction and lymphatic and blood vessel infiltration are demonstrable. These developments have been investigated by light microscopy, histochemistry, transmission- and scanning electron microscopy. (Author abstract) (15 Refs)

13. SPONTANEOUSLY METASTASIZING VARIANTS DERIVED FROM MNU-INDUCED RAT MAMMARY TUMOUR.

Williams JC, Gusterson BA, Coombes RC
Ludwig Inst. Cancer Res., Royal Marsden Hosp., Sutton, Surrey SM2 5PX, England
Br J Cancer; 45(4):588-597 1982

N-methyl-N-nitrosourea (MNU) given iv to female rats of inbred strains induces mammary adenocarcinomas which are hormone-sensitive but do not spontaneously metastasize. Tissue culture and selection techniques have been used to derive metastasizing tumors from a mammary tumor induced with MNU in F344/N rats. Histologically, primary tumors and metastases in the lung and lymph nodes were similar. These systems may constitute useful models for the study of breast-cancer metastasis. (Author abstract) (29 Refs)

14. BIOCHEMICAL CHANGES IN EXPERIMENTAL RAT BRAIN TUMORS INDUCED BY ETHYLNITROSOUREA AND HUMAN GLIOMAS AFTER DIBUTYRYL CYCLIC AMP TREATMENT.

Shibata I, Matsumoto M, Nagasawa S, Seiki Y, Takezawa J
Dept. Neurosurgery, Toho Univ., Sch. Medicine, 6-11-1, Omori-nishi, Ota-ku, Tokyo 143, Japan
Neurol Med Chir (Tokyo); 22(1):1-6 1982

Previous reports have shown that dibutyryl 3',5'adenosine monophosphate (DBc-AMP) suppresses growth of actively dividing tumor cells, accelerates normalization of cellular metabolism and elevates the intracellular level of cyclic AMP. In an effort to study this mechanism further and define its significance, studies were performed on pregnant rats with ethylnitrosourea (ENU) induced gliomas and human subjects with malignant gliomas. RNA and DNA were detected in remarkably high concentrations in the tumor tissue with a significant reduction after treatment with DBc-AMP. The reduction was more pronounced with RNA. Free amino acids were noted in relatively low concentrations in tumor tissue. However, treatment with DBc-AMP resulted in a significant elevation of their value. The levels of glutamic acid, aspartic acid and GABA increased to levels corresponding to the composition of free amino acids in normal brain tissues. Lysosomal enzyme activity in tumor tissue was 10x greater than that in normal brain tissue. This activity dropped significantly after administration of DBc-AMP. In rats with ENU induced glioma, the uptake of radioactive [H3]DBc-AMP by tumor tissue occurred in a volume 2-3x that of normal tissue. However, the ratio of [H3]cyclic AMP/cyclic AMP was less than that in normal tissue, implying that an enhanced synthesis of endogenous cyclic AMP occurs after administration of DBc-AMP. (Author abstract) (22 Refs)

15. PURIFICATION AND TRANSPLANTATION OF HEPATOCYTES FROM LIVERS OF CARCINOGEN-TREATED RATS.

Miller SB, Pretlow TP, Scott JA, Pretlow TG
Dept. Pathology, Univ. Alabama in Birmingham, Birmingham, AL, 35294
JNCI; 68(5):851-857 1982

Young adult male F344 rats were given 90 ppm diethylnitrosamine in drinking water for 5 weeks. Cells were obtained in suspension from the livers of these animals by in situ perfusion of collagenase. Cells were separated in a 2.7-16% (wt/wt) continuous gradient of Ficoll in tissue culture medium in the Sorvall TZ-28 reorienting zonal rotor for 10 minutes at 4 C with a centrifugal force of 12 x g at the sample-gradient interface (26 x g at the gradient-cushion interface). Up to half a billion liver cells were separated without exceeding the band capacity. In all experiments the purest fractions contained more than 90% hepatocytes. After centrifugation, 72.4 +-6.6% of the purified hepatocytes had histochemically demonstrable glutamyl transpeptidase (GGT). When purified hepatocytes were injected into the mesenteric veins of rats given a diet containing 0.02% (wt/wt) N-2-fluorenylacetamide for 7 days and subjected to partial hepatectomy, all rats that received these cells developed foci that exhibited histochemically demonstrable GGT. Hepatocytes with histochemically demonstrable GGT make up all or part of what previously has been referred to as 'liver colony-forming units.' With the TZ-28 reorienting zonal rotor, these cells can be purified in biochemically preparative quantities. (Author abstract) (32 Refs)

16. KINETICS OF PHENOTYPIC MATURATION OF REMODELING OF HYPERPLASTIC NODULES DURING LIVER CARCINOGENESIS.

Enomoto K, Farber E
(c/o Farber) Dept. Pathology, Univ. Toronto, Banting Inst., Toronto, Ontario M5G 1L5, Canada
Cancer Res; 42(6):2330-2335 1982

Hyperplastic nodules appearing during the preneoplastic phase of liver carcinogenesis were divided into two types, persistent and remodeling, according to the pattern of staining for gamma-glutamyltransferase. In the resistant cell model of liver carcinogenesis used in this study, hyperplastic nodules,

uniformly staining for gamma-glutamyltransferase, rapidly emerge by 4 wk after a single injection of diethylnitrosamine and brief selection by dietary 2-acetylaminofluorene plus partial hepatectomy. By 6 wk, a majority of nodules (about 75%) show an obvious irregularity and loss of uniformity in staining for gamma-glutamyltransferase while the remaining nodules continue to be uniformly stained. The number of irregularly stained nodules increases over the next 18 wk until over 95% of nodules show the nonuniform loss of enzyme activity. The progressive loss of enzyme activity is accompanied by architectural remodeling to normal-appearing liver. This is associated with the increasing disappearance of many obvious nodules from the liver as the remodeling ones blend imperceptibly with the surrounding liver. The uniformly stained nodules show the persistence of hepatocyte arrangements in plates two or more cells thick and in acini and of cytoplasmic hypertrophy characteristic of persistent hyperplastic nodules. Labeling indices are much higher in hepatocytes of the persistent uniformly stained nodules than in the remodeling ones. The possibil.. of exploiting this phase of the model further for in-depth analysis of the nodule-to-carcinoma sequence is discussed. (Author abstract) (39 Refs)

17. PROMOTIVE EFFECTS OF STEROIDS AND BILE ACIDS ON HEPATOCARCINOGENESIS INITIATED BY DIETHYLNITROSAMINE.

Cameron RG, Imaida K, Tsuda H, Ito N
(c/o Ito) First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Cancer Res; 42(6):2426-2428 1982

The ability of four steroids and three bile acids to promote the appearance of hyperplastic foci and hyperplastic nodules initiated by diethylnitrosamine (DEN) in the liver of male Fischer rats was tested and compared with that of the known promoter phenobarbital (PB, 0.05%) as a standard value. Two weeks after a single dose of 200 mg of DEN per kg, the animals were exposed to test chemicals for 10 weeks. At 4 weeks following DEN, all treatment groups were subjected to partial hepatectomy. Of the steroids tested at the maximum tolerable doses, as determined in preliminary experiments, ethinyl estradiol was the most potent promoter, inducing more hyperplastic nodules than did PB and almost 50% less gamma-glutamyl transpeptidase-positive foci. However, gamma-glutamyl transpeptidase-positive foci induced by ethinyl estradiol were twice the average size as those induced by PB. The steroids testosterone, cortisone, and dexamethasone induced more foci than did DEN alone, but few if any hyperplastic nodules. Deoxycholic acid was the most potent promoter of the bile acids tested, inducing 3 to 4 times more hyperplastic nodules than did PB and more gamma-glutamyl transpeptidase-positive foci, which were 5 times larger on the average than those induced by PB. The other bile acids tested, lithocholic acid and taurine, induced slightly more foci than did DEN alone but no hyperplastic nodules. These findings suggest that ethinyl estradiol and deoxycholic acid are relatively strong promoters of the appearance of preneoplastic lesions in hepatocarcinogenesis. (Author abstract) (22 Refs)

18. MORPHOLOGIC VARIANTS OF HEPATOCELLULAR CARCINOMA AFTER SMALL DOSES OF HEPATOCARCINOGENS IN RATS WITH REGENERATING LIVER.

Chopra P, Dhar A, Nayak NC
Dept. Pathology, All India Inst. Medical Sciences, New Delhi 110029, India
Indian J Med Res; 74:907-914 1981

Sequential evolution of hepatic neoplasms after administration of one or few small doses of dimethyl-nitrosamine and 2-acetylamino fluorene to rats with regenerating livers has been studied. A number of animals developed hepatocellular carcinoma (HCC). The commonest histologic type was a trabecular HCC. Benign biliary cystadenomas were frequent. Extramedullary hematopoiesis, vacuolation of tumor cells, fatty change and globular hyaline were often associated with HCC. Mallory's hyaline was not encountered. Tumorous and non-tumorous proliferation of Kupffer cells was a notable feature. Irrespective of the type and extent of HCC, no metastases were encountered. (Author abstract) (23 Refs)

19. THY-1 ANTIGEN ON NORMAL AND NEOPLASTIC RAT MAMMARY TISSUES: CHANGES IN LOCATION AND AMOUNT OF ANTIGEN DURING DIFFERENTIATION OF CULTURED STEM CELLS.

Rudland PS, Warburton MJ, Monaghan P, Ritter MA
Ludwig Inst. Cancer Res. (London Branch), Royal Marsden Hosp., Sutton, Surrey, SM2 5PX, England
JNCI; 68(5):799-811 1982

With the use of immunofluorescent and immunocytochemical techniques on histologic sections of mammary glands from inbred WF rats, the thymocyte differentiation antigen (Thy-1) was identified partially on and immediately adjacent to the myoepithelial cells of ducts and alveoli. This antigen was absent from epithelial cells lining such structures. Some fibroblastic cells external to these structures also bore Thy-1. During glandular development the intensity of fluorescence due to the binding of Thy-1 antibodies increased as the myoepithelial cells matured. Similarly, mammary adenocarcinomas induced by 7,12-dimethylbenz[a]anthracene (DMBA) and N-methyl-N-nitrosourea contained elongated, presumptive myoepithelial cells that demonstrated varying degrees of Thy-1 immunofluorescence. This phenomenon was qualitatively mimicked by cultured cell lines from normal and DMBA-induced tumors. Elongated myoepithelial-like and fibroblast-like cells possessed Thy-1, whereas the cuboidal epithelial cell lines failed to express this antigen on the cell surface. Measurement of the relative number of Thy-1 molecules per cell by antiserum absorption techniques suggested that a neoplastic stem cell line, rat mammary (Rama) 25, contained about 3 x 10(5) Thy-1 molecules per cell in a form not directly accessible at the cell surface to anti-Thy-1 antibodies; the number of cryptic Thy-1 molecules was reduced when this cell line differentiated to alveolar-like cells in culture. However, when this cell line differentiated to myoepithelial-like cells, approx 5 x 10(6) molecules per cell were exposed to anti-Thy-1 antibodies with a concomitant reduction of the cryptic pool. Morphologic maturation of elongated, myoepithelial-like cell line variants was also accompanied by increased surface Thy-1 fluorescence. Thus some of the myoepithelial cells in normal glands and tumors may arise by differentiation of epithelial stem cells and a spectrum of maturation states of the myoepithelial cell may exist as monitored by cellular morphology and surface Thy-1 expression. (Author abstract) (44 Refs)

20. IN VIVO BINDING OF N-NITROSOPYRROLIDINE AND N-NITROSOHEXAMETHYLENEIMINE TO NON-PURINE SITES ON RAT LIVER DNA.

Ross AE, Lawson TA

Eppley Inst. for Res. in Cancer, Univ. Nebraska Medical Center, Omaha, NE, 68105

Cancer Lett; 15(3):329-334 1982

Treatment of male MRC-Wistar rats with labeled N-nitrosopyrrolidine (NPYR) and N-nitrosohexamethyleneimine (NHX) is reported. Radioactivity profiles of the 70% perchloric acid hydrolysates of liver DNA and RNA from [3H]NHX-treated rats after cation exchange are presented. The main peak is in the same numbered fraction for both DNA and RNA, and is apparently volatile, since 90% was lost on evaporation to dryness in current nitrogen. Chromatography of DNA and RNA hydrolysates on Sephadex G-10 produced similar radioactive profiles and resulted in a single major peak of volatile substance in corresponding fractions. The results contrast with the radioactive components (RC) separated by cation exchange chromatography of 1 M HCl hydrolysates of the nucleic acids from NHX-treated rats. RNA yielded five main RC. DNA had only four RC, with 5% of the radioactivity in a peak at the same elution vol as 1,6-hexane-diol. The chromatogram of the DNA mild acid hydrolysate from NPYR-treated rats had an identical feature. These results suggest that either the two nitrosamines do not interact with purines or, if purine interaction takes place, the groups attached to the purine alter their chromatographic properties to such an extent that they elute from a Sephadex G-10 column with apurinic acid. Experiments were performed to test this hypothesis and the results obtained suggest that radioactivity was still attached to the large-mol-wt apurinic acid remaining in the dialysis tubing. The data could be due to alkylation that took place only at the phosphate groups or to a metabolite produced from NHX with two active sites, capable of forming cross-links. The findings suggest that extensive phosphotriester formation and/or cross-link formation might be a feature common to DNA alkylated by alicyclic nitrosamines. (9 Refs)

21. NONHISTONE PROTEINS OF RAT LIVER TRANSFORMED BY NITROSODIETHYLAMINE.

Seits IF, Glebov AV

N. N. Petrov Res. Inst. Oncology, USSR Ministry Health, Leningrad, USSR

Vopr Onkol; 28(1):42-46 1982

Qualitative and quantitative content of nonhistone chromosomal proteins (NHP) from normal and nitrosodiethylamine-transformed rat liver was studied. An increase in the protein/DNA ratio in tumor chromatin, as compared with that of normal tissue, was established. NHP were extracted from the chromatin with 0.4 N N2SO4 and fractionated with two-dimensional polyacrylamide gel electrophoresis. Coomassie staining revealed more than 80 fractions with mol wt ranging 20-150 th. Some quantitative and qualitative differences in the patterns of NHP from normal and neoplastic tissues were observed. A conclusion is drawn that these differences may be related to structural and/or enzymatic components of NHP. (Author abstract) (17 Refs) (In RUS)

22. ACID HYDROLASES AND TUMOR INVASION. RELATIONSHIP BETWEEN INTRACELLULAR DISTRIBUTION OF HYALURONIDASE, CATHEPSIN D AND ACID PHOSPHATASE, AND CELL PROLIFERATION, IN RAT LIVER AND DIETHYLNITROSAMINE-INDUCED HEPATOMA.

Fiszer-Szafarz B

Institut Curie-Biologie, Batiment 111, Centre Universitaire, 91405 Orsay, France

Biol Cell; 42(2/3):97-102 1981

The distribution of acid phosphatase (E.C. 3.1.3.2) and cathepsin D (E.C. 3.4.4.23) activities in the subcellular fractions is different in diethylnitrosamine-induced hepatoma in rat from that in normal liver. These activities are decreased in lysosomes and increased in microsomes and in the soluble fraction; it is striking that hyaluronidase (E.C. 3.2.1.35) could be detected only as faint traces in the soluble fraction of the tumor cells. The time interval between two successive cell divisions in hepatoma was calculated to be between 50 and 175 hr. The time necessary for the dismantled lysosomal apparatus to be reconstituted is thus not available, as this process takes a much longer time (about 500 hr). The lysosomal enzyme depletion can thus result from these two concurring phenomena. Since the soluble fraction also contains the extracellular fluid, its increased acid phosphatase and cathepsin D proportions, along with its small hyaluronidase content, are in some way similar to the increase in hyaluronidase activity which we had observed in Walker carcinoma 256 interstitial fluid. These increases suggest the possible role of these enzymes in the invasive capacity of malignant tumors. (Author abstract) (30 Refs)

23. CARCINOGENICITY TESTS OF ACETOXYMETHYLPHENYLNITROSAMINE AND BENZENEDIAZONIUM TETRAFLUOROBORATE IN SYRIAN HAMSTERS.

Gold B, Salmasi S

Eppley Inst. for Res. in Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105

Cancer Lett; 15(3):289-300 1982

The bioassay of acetoxymethylphenylnitrosamine (AMPhN) and benzenediazonium tetrafluoroborate (BDI-BF4) by sc injection and of BDI-BF4 by gavage in Syrian golden hamster is reported. The LD50 of AMPhN was determined by sc injection of olive oil vehicle to be 134.0 mg/kg and 116.6 mg/kg in females and males, respectively. Animals were injected weekly sc with AMPhN in olive oil at 12.5, 6.25, and 3.13 mg/kg, which corresponded to 1/10, 1/20, and 1/40 av acute LD50. At the two higher doses, animals developed serious sores at the injection site and treatment was terminated after 4 wk for these two dose groups. A lower dose of 1.56 mg/kg was then initiated. Results of the experiment are presented. The acute LD50 of BDI-BF4 in hamsters by sc injection in 0.9% saline was 166.2 mg/kg and 219.2 mg/kg in females and males, respectively. For chronic testing, freshly prepared solutions of BDI-BF4 were injected sc weekly at 19, 9.5, and 4.75 mg/kg. One control group received sc injections of saline solutions and another 11.5 mg/kg of sodium tetrafluoroborate in 0.9% saline, a dose corresponding to the molar equivalent of the highest dose of BDI-BF4 used. At these three doses of BDI-BF4, the hamsters rapidly developed open sores at the injection sites and the treatment was halted after 10 wk. An additional two doses at 2.38 mg/kg and 1.19 mg/kg were started and these animals were treated for life. BDI-BF4 was less toxic by intragastric administration, with the acute LD50 being 353.7 mg/kg for

both females and males. No significant qualitative or quantitative difference in tumors was found between treated and control animals in this experiment. (37 Refs)

24. TREATMENT OF SMALL-CELL CARCINOMA OF THE LUNG MONITORED BY SEQUENTIAL FLOW CYTOMETRIC DNA ANALYSIS.

Vindelov LL, Hansen HH, Gersel A, Hirsch FR, Nissen NI
Dept. Internal Medicine, Finsen Inst., 49 Strandboulevarden, DK-2100 Copenhagen, Denmark
Cancer Res; 42(6):2499-2505 1982

Treatment-induced cell-kinetic changes in patients with small-cell carcinoma of the lung were studied, with the objective of exploiting the changes for improving the treatment. Flow-cytometric DNA analyses on fine-needle aspirates of metastases were used to monitor the cell cycle perturbations. Volume changes of metastases were determined by caliper measurements, and the white blood cell counts were used as an indicator of the toxicity. Fourteen metastases in 11 patients were studied during a total of 14 courses of treatment with cyclophosphamide, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, vincristine, and methotrexate. The cell cycle changes preceded tumor reduction. They consisted of a relative decrease in G1 cells starting on Day 1, maximal on Days 3 to 5. Simultaneously, there was an increase in the S phase. This was followed in some patients by an increase in G2 + M starting on Day 3, maximal on Days 4 to 6. The maximal changes observed in the cell cycle were: G1 70% to 1%, S, 32% to 90%; and G2 + M, 14% to 88%. The tumor volume changes started on Day 2 and were highly variable, ranging from a brief partial remission to a complete remission. In contrast, the time course of the white blood cell count changes were fairly uniform. Two indices, designated the sensitivity index and the therapeutic index, were calculated to compare quantitatively the tumor volume changes and the white blood cell count changes. The pretreatment S-phase size was used as an indicator of proliferative activity. The evidence indicated that differences in tumor sensitivity were responsible for the variable initial tumor reduction. a large initial cell kill did not guarantee a successful outcome of the treatment. A previously demonstrated heterogeneity of individual tumors is a likely explanation for this phenomenon. (Author abstract) (15 Refs)

MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS

25. ORGAN-SPECIFIC PROMOTING EFFECTS OF PHENOBARBITAL SODIUM AND SODIUM SACCHARIN IN THE INDUCTION OF LIVER AND URINARY BLADDER TUMORS IN MALE F344 RATS.

Nakanishi K, Fukushima S, Hagiwara A, Tamano S, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizucho-cho, Mizuho-ku, Nagoya 467, Japan
JNCI; 68(3):497-500 1982

Studies were conducted to determine whether initial treatment with N-2-fluorenylacetamide (2-FAA) or N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) followed by treatment with either phenobarbital sodium (PB) or sodium saccharin (SS) induced or enhanced liver and/or bladder tumorigenesis. Male inbred F344 rats were given 0.05% PB and 5.0% SS in the diet for 32 wk after 4-wk administration of 0.02% 2-FAA or 0.01% BBN. PB significantly enhanced hepatocarcinogenesis after 2-FAA treatment and induced hyperplastic liver nodules after BBN treatment. The SS significantly enhanced induction of bladder hyperplasias, but not papilloma after BBN treatment, and induced bladder hyperplasias after 2-FAA treatment. However, PB had no effect on the bladder and SS had no effect on the liver after either 2-FAA or BBN treatment. The data indicate that although 2-FAA and BBN have tumor-initiating effects in the liver and urinary bladder, the tumor-promoting effects of PB and SS are organ-specific. The tumor-promoting effect of PB for the liver is relatively greater than that of SS for the urinary bladder. (Author abstract) (25 Refs)

26. PROGRESSION OF CARCINOGEN-INDUCED FOCI OF GAMMA-GLUTAMYLTRANSPEPTIDASE-POSITIVE HEPATOCYTES TO HEPATOMAS IN RATS FED A CHOLINE-DEFICIENT DIET.

Takahashi S, Lombardi B, Shinozuka H
(c/o Shinozuka) Dept. Pathology, Univ. Pittsburgh Sch. Medicine, Pittsburgh, PA, 15261
Int J Cancer; 29(4):445-450 1982

Following previous findings that feeding a choline-deficient (CD) diet to rats strongly promotes the evolution of liver cells, initiated by a chemical carcinogen, to foci of gamma-glutamyltranspeptidase (gammaGT)-positive hepatocytes, we investigated whether a CD diet could also promote the evolution of gammaGT-positive foci to hepatomas. GammaGT-positive foci were induced in male Sprague-Dawley rats by administration of a single dose of diethylnitrosamine followed by 2 wk feeding on a CD diet containing 0.02% acetylaminofluorene. Immediately thereafter, one group of rats was fed a plain CD diet and the other a choline-supplemented (CS) diet, and subgroups of animals were killed periodically for analysis of the number and size of gammaGT-positive foci and development of hepatomas. During the first 7 wk after switching the diets, the number and size of the foci increased in both groups. At 12 and 16 wk, the number and size of foci began to decline in rats fed the CS diet. However, in the CD group, there was a progressive increase in the size with coalescence of the foci, as well as development of neoplastic nodules. These lesions were followed at 20 and 28 wk by development of hepatomas at a high incidence rate. In rats fed the CS diet, a few scattered gammaGT-positive foci, and small neoplastic nodules remained in the liver at 20 and 28 wk, but no hepatomas developed. These results show that the CD diet is a potent promoter of the evolution of foci of altered hepatocytes to hepatomas, and that most of the gammaGT-positive foci are reversible lesions. (Author abstract) (37 Refs)

27. COMPARISON OF ENHANCEMENT OF GGTASE-POSITIVE FOCI AND INDUCTION OF ORNITHINE DECARBOXYLASE IN RAT LIVER BY BARBITURATES.

Pereira MA, Savage RE, Herren SL, Guion CW
Health Effects Res. Lab., United States Environmental Protection Agency, 26 West St. Clair St., Cincinnati, OH, 45268
Carcinogenesis; 3(2):147-150 1982

The induction of ornithine decarboxylase (ODC) by barbiturates and the ability of barbiturates to enhance neoplastic progression of chemically initiated cancer was examined in rat liver. All seven barbiturates induced ODC with barbital (7.7 fold increase) and phenobarbital (5.7 fold increase) demonstrating the most potent activity. Maximum induction of ODC by phenobarbital was obtained in 18 h, Barbital (500-5,000 ppm) and phenobarbital (500 ppm) administered in the drinking water enhanced the appearance of diethylnitrosamine

(DENA)-initiated gamma-glutamyltranspeptidase (GGTase)-positive foci. Amobarbital, hexabarbital and pentobarbital did not enhance the appearance of GGTase-positive foci. In the absence of previous initiation by DENA, the enhancing regimen of the barbiturates did not cause the appearance of GGTase-positive foci. Barbiturates induced ODC activity in rat liver and enhanced the incidence of DENA initiated GGTase-positive foci. (Author abstract) (24 Refs)

28. THE KINETICS OF THE PROTECTIVE EFFECT OF BETA-SITOSTEROL AGAINST MNU-INDUCED COLONIC NEOPLASIA.

Deschner EE, Cohen BI, Raicht RF
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
J Cancer Res Clin Oncol; 103(1):49-54 1982

The effect of dietary supplementation with beta-sitosterol (0.2% of diet) was followed in Fischer rats after both acute and chronic feeding. Compared to controls after 3 and 7 days, the number of epithelial cells per crypt column in both plant sterol fed groups was shifted to lower values; moreover, fewer cells above cell position 12 were engaged in DNA synthesis. Continued feeding of beta-sitosterol for 28 wk revealed the number and position of 3HTdR-labeled cells per crypt column after 1 hr pulse labeling to be similar to that seen in the acute phase. However, differences were more marked after 24 hr showing the max number of labeled cells per column to be at least 25% less than the untreated group and the leading edge of labeled cells moving more slowly up the crypt wall. Rats treated with N-methyl-N-nitrosourea (MNU) intrarectally (8 mg/animal) while simultaneously consuming beta-sitosterol demonstrated a reduction in the size of the proliferative compartment as well as the number of labeled cells per crypt column as compared to rodents receiving just the carcinogen (3.3 and 5.4 mean labeled cells per column, respectively). At this time, MNU-treated rats fed beta-sitosterol had a significantly decreased colonic tumor incidence. This plant sterol which passes through the digestive tract relatively unabsorbed appears to slow colonic epithelial cell proliferation resulting in a reduced expression of neoplastic transformation. (Author abstract) (6 Refs)

29. EFFECTS OF HYPOTHYROIDISM ON DEVELOPMENT OF NITROSOMETHYLUREA-INDUCED TUMORS OF THE MAMMARY GLAND, THYROID GLAND, AND OTHER TISSUES.

Milmore JE, Chandrasekaran V, Weisburger JH
(c/o Weisburger) American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Proc Soc Exp Biol Med; 169(4):487-493 1982

Female Fischer 344 rats were injected iv with 50 mg/kg N-nitrosomethylurea (NMU) at 50 days of age; some also received 0.3, 1.0, or 3.0 mg propylthiouracil (PTU) per 100 ml of drinking water, beginning 5 days after the NMU administration, and others received 131I injections. Six wk after treatment, serum thyroxine levels were elevated in rats receiving NMU only, but not in those receiving PTU as well, whereas a 10 uCi dose of 131I caused a slight but significant depression of serum thyroxine level. PTU or 131I increased the incidence of benign and 1 malignant mammary tumors, except in rats receiving the highest PTU dose, which had a decreased incidence of malignancies. Weights of ovaries, uteri, or adrenal glands were unaffected by NMU or PTU. Malignant neoplasms were adenocarcinomas that were sometimes multiple. Benign thyroid tumors were follicular adenomas; malignant thyroid tumors were mostly follicular, or follicular mixed with papillary carcinoma. Numerous other neoplasms appeared in other systems. Slight hypothyroidism could increase the incidence of NMU-induced mammary tumors in the rat, but when hypothyroidism was severe enough to limit growth, tumor incidence was less. (32 Refs)

30. PROSTAGLANDIN SYNTHESIS AND BINDING IS INCREASED IN REGRESSING NMU MAMMARY CARCINOMA.

Liu SC, Knazek RA
Lab. Pathophysiology, NCI, NIH, Bethesda, MD
Prostaglandins Leukotrienes Med; 8(3):191-198 1982

Nitrosomethylurea-induced mammary tumors of Buffalo rats were used to study the regression after oophorectomy (oox). The amounts of prostaglandin E2 (PGE2) and prostaglandin F2 alpha (PGF2a) isolated from tumor cell membranes increased during the period of tumor growth, peaking 5 days after oophorectomy. The membrane binding of both prostaglandins (PGs) was saturable and reversible, reaching equilibrium after 30 min. The membrane binding of both PGs was 3-4x above baseline values on day 4 after oox. The membrane binding of PGE2 showed low-affinity characteristics during both tumor growth and oox-induced tumor regression. The membrane binding of PGF2a showed high-affinity characteristics during both tumor growth and oox-induced tumor regression; the post-oox increase in specific PGF2a binding was attributed to an increase in the number of PGF2a receptors. The elevated rates of PGF2a synthesis and the regression-associated increase in PGF2a receptors suggest that PGF2a may play a significant role in hormone-dependent mammary tumor regression. (22 Refs)

31. ZINC DEFICIENCY, ALCOHOL, AND A RETINOID: ASSOCIATION WITH ESOPHAGEAL CANCER IN RATS.

Gabrial GN, Schrager TF, Newberne PM
(c/o Newberne) Animal Pathology Lab., Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
JNCI; 68(5):785-789 1982

Groups of Charles River Sprague-Dawley male rats were given intragastric intubations of methylbenzylnitrosamine after receiving one of the following diets for 4 weeks: control, zinc-deficient, or zinc-deficient diet plus 4% ethanol in the drinking water. One zinc-deficient group was zinc repleted after the dosing period; the other group, zinc-deficient plus 4% ethanol, received 13-cis-retinoic acid (13-cis-RA) after the dosing period. Zinc deficiency significantly enhanced esophageal tumor incidence; the addition of ethanol further enhanced tumor incidence. Zinc repletion reduced tumor incidence, whereas the addition of 13-cis-RA enhanced tumor incidence. (Author abstract) (30 Refs)

32. INHIBITION OF CHEMICAL CARCINOGENESIS BY RETINOIDS.

Moon RC, McCormick DL
Life Sciences Div., IIT Res. Inst., 10 West 35th St., Chicago, IL, 60616
J Am Acad Dermatol; 6(4,part2):809-814 1982

Experiments involving two-stage skin carcinogenesis in mice, the induction of bladder tumors in rats or mice by N-methyl-N-nitrosourea (MNU) or N-butyl-N-(4-hydroxybutyl)nitrosamine (OH-BBN), the induction of mammary tumors in rats by MNU, and the induction of esophageal

tumors in rats by N-methyl-N-benzylnitrosamine have demonstrated several important structure-activity relationships in the inhibition of chemical carcinogenesis by retinoids. The aromatic ring, side chain, and polar terminal groups of the retinoid molecule have important effects on the agent's organ distribution and thus its anticarcinogenic activity. Retinoids that significantly inhibit OH-BBN bladder carcinogenesis include 13-cis-retinoic acid (c-RA), ethyl retinamide, 13-cis-ethyl retinamide, 2-hydroxyethyl retinamide, 4-hydroxyphenyl retinamide (4-HPR), 13-cis-4-hydroxyphenyl retinamide, and 2-hydroxypropyl retinamide. Retinoic acid (RA) is a less favorable preventer of MNU-induced mammary tumors in rats than 4-HPR, because 4-HPR accumulates to a lesser extent in the liver and so is less hepatotoxic than RA. Synergistic interactions between retinoids (eg, RA or 4-HPR) and hormonal treatments in MNU mammary carcinogenesis have been discovered. Retinoid treatment from the time of carcinogen administration or the first excision of a carcinogen-induced tumor has greater chemopreventive activity than delayed treatment. The efficacy of delayed retinoid treatment largely depends on the tumor's latent period. The authors' current research involves the identification of new retinoids having lower toxicity and higher chemopreventive activity, combination treatments having synergistic antitumor activity, and the mechanisms of action of the retinoids. (28 Refs)

33. RESPIRATORY TRACT TUMOURS IN HAMSTERS EXPOSED TO ACETALDEHYDE VAPOUR ALONE OR SIMULTANEOUSLY TO BENZO(A)PYRENE OR DIETHYLNITROSAMINE.

Feron VJ, Kruysse A, Woutersen RA
Inst. CIVO-Toxicology and Nutrition TNO, P.O. Box 360, 3700 AJ Zeist, The Netherlands
Eur J Cancer Clin Oncol; 18(1):13-31 1982

Syrian golden hamsters were exposed to 0 or 2,500-1,650 ppm acetaldehyde vapor, 7 hr/day, 5 days/wk for a period of 52 wk. A proportion of the animals was given, simultaneously, either intratracheal instillations of benzo(a)pyrene (BP) or sc injections of diethylnitrosamine (DENA). All treatments were stopped after 52 wk. The study was terminated after 81 wk. Major effects attributed to acetaldehyde exposure included growth retardation, rhinitis, hyperplasia and metaplasia of the nasal, laryngeal and tracheal epithelium, nasal and laryngeal carcinomas, and a markedly increased incidence of BP-initiated tracheobronchial carcinomas. There was no evidence of acetaldehyde enhancing the development of DENA-initiated tumors of the respiratory tract. It was concluded that acetaldehyde is an irritant, as well as a carcinogen, for the respiratory tract of Syrian golden hamsters. Possible mechanisms of the carcinogenicity of this aldehyde are briefly discussed. (Author abstract) (15 Refs)

MUTAGENICITY OF NITROSO COMPOUNDS

34. RESISTANCE OF SALMONELLA TYPHIMURIUM TA 1535 TO O(6)-GUANINE METHYLATION AND MUTAGENESIS INDUCED BY LOW DOSES OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE: AN APPARENT CONSTITUTIVE REPAIR ACTIVITY.

Guttenplan JB, Milstein S
Dept. Biochemistry, New York Univ. Dental Center, 345 E. 24th St., New York, NY, 10010
Carcinogenesis; 3(3):327-331 1982

Salmonella tester strains which are reverted by base-pair substitution mutagens are relatively insensitive to the mutagenic effects of N-methyl-N-nitroso compounds. One reason for this insensitivity is the ability of these strains to withstand low doses of these compounds before they become sensitive to their mutagenic effects. In this report it is shown that mutagenesis induced by treatment of Salmonella typhimurium TA 1535 with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in buffer is biphasic with a low sensitivity range at low doses where little mutagenesis occurs, followed by a high sensitivity range whose onset begins after an apparent threshold dose has been exceeded. Levels of O6-methylguanine (O6-MeG) in the DNA extracted from the bacteria follow a similar dose-response curve suggesting a dependency of mutagenesis on O6-MeG. In contrast, levels of 7-methylguanine (7-MeG) in the DNA increase linearly with dose. O6-MeG was undetectable at the lowest dose of MNNG whereas 7-MeG was readily detectable. Although such resistance to O6-alkylation has been demonstrated in MNNG-pretreated (adapted) E coli, it has not been reported in unpretreated cells. When isolated DNA was treated with MNNG a linear dose-response in the generation of O6-MeG was observed. The lack of O6-MeG in DNA isolated from MNNG treated cells after low doses is attributed to a saturable, constitutive repair activity in the bacteria. An attempt to observe the removal of O6-MeG from the bacteria after exposure to a short challenge dose of N-nitroso-N-methylurea (NMU) followed by a subsequent incubation in buffer was unsuccessful, probably because all the repair occurred within the time necessary to treat and lyse the cells. (Author abstract) (22 Refs)

35. INDUCTION OF SISTER-CHROMATID EXCHANGES BY INDIRECT MUTAGENS/CARCINOGENS IN CULTURED RAT HEPATOMA AND ESOPHAGEAL TUMOR CELLS AND IN CHINESE HAMSTER DON CELLS CO-CULTIVATED WITH RAT CELLS.

Abe S, Sasaki M
(c/o Sasaki) Chromosome Res. Unit, Faculty Science, Hokkaido Univ., North 10, West 8, Sapporo, Hokkaido 060, Japan
Mutat Res; 93(2):409-418 1982

The inducibility of sister-chromatid exchanges (SCEs) in rat ascites hepatoma (AH66-B) and a rat esophageal tumor (R1) cell line by 2-acetylaminofluorene, butylbutanolnitrosamine, cyclophosphamide, urethane, 4-aminoazobenzene, 2-methyl-4-dimethylaminoazobenzene, 3'-methyl-4-dimethylaminoazobenzene, 4-o-tolyazo-o-toluidine, benzo(a)pyrene, 7,12-dimethylbenzyl(a)anthracene, 3-methylcholanthrene, and diethylstilbestrol (DES) was studied. Six of the chemicals were used with a cell-mediated system using Chinese hamster Don-6 cells as the target cells and co-cultivated AH66-B or R1 cells as the metabolizing feeder layer. Out of 14 indirect mutagens/carcinogens tested, 11, including 5 amine derivatives, 3 azo compounds, 2 aromatic hydrocarbons and 1

steroid, induced SCEs in AH66-B and/or R1 cells. The frequency of SCEs in Don-67 cells exposed to 6 selected chemicals was substantially enhanced in the presence of AH66-B or R1 cells. For some chemicals, especially aromatic hydrocarbons, the doses required to induce SCEs in AH66-B and R1 cells were much higher than those reported for some other cell systems. Certain chemicals, eg, DES, were active inducers of SCEs in the present systems, but are known to be inactive in microbial and other test systems. The two approaches described represent simple and reliable screening assays in vitro for detection of indirect mutagens/carcinogens. (32 Refs)

36. SCE AND UDS STUDIES IN A FAMILY WITH RETINOBLASTOMA: A CASE STUDY.

Fabricant JD, Au W, Fabricant RN, Morgan KS
Dept. Preventive Medicine and Community Health, Div. Genetic Toxicology, Univ. Texas Medical Branch, Galveston, TX
Teratogenesis Carcinog Mutagen; 2(1):85-90 1982

Lymphocytes from a father and daughter with retinoblastoma were analyzed for spontaneous and mitomycin C (MMC)-induced sister chromatid exchanges (SCE) and unscheduled DNA synthesis (UDS) induced by MMC and M-methyl-N-nitro-N-nitrosoguanidine (MNNG), compared to results from two controls. Cells for the SCE studies were treated with 10(-8) and 10(-7) M MMC, and those for the UDS studies with 0.3-10 ug/ml MMC or 1-30 x ug/ml MNNG. SCE were identified after staining by the fluorescent-plus Giemsa technique, and UDS by incorporation of 3H-thymidine. Spontaneous and induced SCE frequencies were similar in retinoblastoma and control lymphocytes. UDS was the same for both groups after MMC treatment, but was not increased in the experimental group after MNNG treatment, as compared to an increase seen in the control group. Results indicate that lymphocytes from retinoblastoma patients respond normally to the cross-linking agent MMC, but are unable to repair DNA damage caused by the alkylating agent MNNG. (18 Refs)

37. VARIATIONS AMONG SPECIES AND CELL TYPES IN THE EFFECTS OF CAFFEINE ON MUTAGEN-INDUCED CYTOTOXICITY AND POSTREPLICATION REPAIR OF DNA.

Sivak A, Rudenko L, Teague LG
Arthur D. Little, Inc., Cambridge, MA, 02140
Environ Mutagen; 4(2):143-162 1982

Caffeine effects in culture of rodent and human cells are reviewed, and the effects of caffeine on postreplication repair induced by chemical mutagens in normal human fibroblasts (HS-WP), human xeroderma pigmentosum fibroblasts (SGL), mouse BALB/c-3T3 fibroblasts, Syrian hamster embryo cells (SHE), and Chinese hamster V79 cells are reported. Cells were exposed to UV light (100 ergs/square mm), nitroquinoline-N-oxide (NQO: 2.5 uM), N-acetoxy-N-2-fluorenylacetamide (AFFA: 2.0 uM), and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG: 50.0 uM) and then to caffeine (0.05-1.0 milliM). Cytotoxicity was enhanced by addition of caffeine to V79 cells and BALB/c-3T3 cells after exposure to either UV light or AFAA. Postreplication repair of V79 cells was inhibited in cells exposed to UV and AFFA. Postreplication repair was not affected by caffeine at concentrations up to 1.0 milliM in HS-WP, SGL, SHE and mouse BALB/c-3T3 cells after exposure to UV, AFAA, NQO, or MNNG. Repair in BALB/c-3T3 cells exposed to UV or AFAA was also unaffected. The failure of cytotoxicity results to agree with repair results for most of these cells indicates that it is incorrect to use cytotoxicity evidence for caffeine to imply that genetic damage has occurred. (49 Refs)

38. INDUCED CHROMOSOME LOSS FOLLOWING TREATMENT OF POSTMEIOTIC CELLS OF THE DROSOPHILA MELANOGASTER MALE WITH MMS AND DMN AND MATINGS WITH REPAIR-PROFICIENT FEMALES AND REPAIR-DEFICIENT FEMALE MEI-9A AND ST MUS302.

Zimmering S
Div. Biology and Medicine, Brown Univ., Providence, RI, 02912
Mutat Res; 94(1):79-86 1982

Frequencies of complete and partial loss of the Y chromosome in Drosophila melanogaster ring-X males treated with methylmethanesulfonates (MMS) or dimethylnitrosamine (DMN) and mated with repair-proficient females or the repair-deficient females, mei-9a and st mus302, are reported. When males were treated with MMS and mated with the repair-deficient females, significant enhancement of induced complete loss (CL) and partial loss (PL) above controls was observed. Frequencies of induced loss were 10x higher with st mus302 than mei-9a. The same trends were observed with DMN. It was observed that st mus302 females were equally sensitive to MMS and DMN-induced break/pre-break lesions, while mei-9a females were less sensitive to MMS- than to DMN-induced lesions. Of 37 PLs observed in the mei-91 series, 13 were mosaics; of 50 with st mus 302, only one was a mosaic. The same phenomenon was observed for procarbazine and diethylnitrosamine (DEN). St mus302 females were more sensitive than mei-9a females and markedly more sensitive than repair-proficient females regarding the recovery of CLs and PLs in tests of procarbazine, DEN, MMS and DMN. Frequencies of chromosome loss are substantially higher with MMS and DMN than procarbazine and DEN. (6 Refs)

39. INDUCTION OF A DNA GLYCOSYLASE FOR N-METHYLATED PURINES IS PART OF THE ADAPTIVE RESPONSE TO ALKYLATING AGENTS.

Karran P, Hjelmgren T, Lindahl T
Imperial Cancer Res. Fund, Mill Hill Lab., Burtonhole Lane, London MW7 1AD, England
Nature; 296(5859):770-773 1982

Adaptation to repetitive DNA alkylation was investigated in Escherichia coli. Only 3-methyladenine DNA glycosylase II, 3-methylguanine DNA glycosylase and 7-methylguanine DNA glycosylase activities were induced during adaptation by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) treatment. These inducible enzyme activities may be associated with a single enzyme, as the relative levels of induction of the three activities were similar. Separation of these activities was not effected by a variety of chromatographic procedures (diethylaminoethanol-cellulose, Sephadex gel chromatography, DNA-cellulose). 3-Methylguanine was removed slowly in unadapted cells, with 50% remaining in DNA 30 min after treatment with MNNG; in adapted cells, however, about 50% was removed immediately during exposure to mutagen, and by 30 min no residual 3-methylguanine was detected. 3-Methyladenine remained in DNA in both cases. 7-Methyladenine and 1-methyladenine were inefficiently removed in adapted and unadapted cells. These results indicate that 3-methylguanine is responsible for a major part of the cytotoxic effect of methylating agents. (25 Refs)

40. ADAPTATION TO ALKYLATION RESISTANCE INVOLVES THE INDUCTION OF A DNA GLYCOSYLASE.

Evensen G, Seeberg E
Inst. General Genetics, Univ. Oslo, Blindern, Oslo 3, Norway
Nature; 296(5859):773-775 1982

The possibility of two pathways for repair of 3-methyladenine residues in Escherichia coli DNA was examined. The first pathway appears to be constitutively expressed and controlled by the gene tag, the second inducible and controlled by ada. Adaptive treatment with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), used to induce 6-methylguanine DNA methyltransferase, also induced high levels of 3-methyladenine DNA glycosylase activity in the tag mutant (BK2114). This induction was not seen in the tag ada double mutant (BK2106). BK2114 additionally regained its ability to reactivate alkylated phages. These results indicate the induction of two separate enzymes for repair of alkylated DNA: 6-methylguanine DNA methyltransferase and 3-methyladenine DNA glycosylase. Both of these enzymes appear under ada control. Since the ada mutation prevents induction of these two separate repair enzymes, the ada gene may be a control gene for the adaptive response. Structural genes for one or both enzymes may be situated elsewhere on the chromosome. Another mutant, alk-1, was found deficient in the induction of TagII but proficient in induction of the methyltransferase. 6-Methylguanine DNA methyltransferase is thought responsible for mutagenic adaptation, while ada+-dependent inducible glycosylase may be responsible for killing adaptation, because DNA polymerase I is required to complete repair of the apurinic site formed by glycosylase action. (14 Refs)

41. MISMATCH CORRECTION AT O6-METHYLGUANINE RESIDUES IN E. COLI DNA.

Karran P, Marinus MG
Imperial Cancer Res. Fund, Mill Hill Laboratories, Burtonhole Lane, Mill Hill, London NW7 1AD, England
Nature; 296(5860):868-869 1982

Escherichia coli dam mutants, which lack the major DNA adenine methylase and are hypersensitive to base analog mutagens, were found to be sensitive to the DNA methylating agent N-methy-N'-nitro-N-nitrosoguanidine (MNNG), which introduces O6-methylguanine (m6G) into DNA. The sensitivity was not observed using methylating agents which generate only low amounts of m6G. The introduction of either mutL or mutS mutation (second site mutations which are also part of the correction system) into dam strains abolished the sensitivity to MNNG. The results suggest that mismatch correction occurs at m6G residues in DNA. (16 Refs)

42. ANAPHASE ABERRATIONS: A MEASURE OF GENOTOXICITY IN MUTAGEN-TREATED FISH CELLS.

Kocan RM, Landolt ML, Sabo KM
Dept. Pathology, SM-30, Univ. Washington, Seattle, WA, 98195
Environ Mutagen; 4(2):181-189 1982

A continuous culture line of rainbow trout gonad (RTG-2) cells was exposed to benzo(a)pyrene (BAP), 3-methylcholanthrene (3MC), anthracene, 1-naphthol, 9-aminoacridine (9AA), mitomycin C (mit-C), and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). During exposure cells were examined for the presence of abnormalities in chromosome arrangement of anaphase figures during mitosis, and were compared to the effects of only solvent (dimethylsulfoxide). Both BAP and 3MC elevated the number of anaphase abnormalities, with more effect at 48 hr than at 24 hr. MNNG, mit-C, and 9AA were also effective in increasing the number of abnormalities. Abnormalities included mainly attached fragments, acentric fragments and bridges, with some side-arm bridges and multipolar cells. Toxicity and inhibition of cell division were also observed with all compounds. No increase in chromosomal lesions was observed in cells treated with naphthol or anthracene, suggesting that each chemical's characteristics, not the chemical class to which it belongs, are important in mutation induction. The in vitro RTG-2 cell system has a highly active mixed function oxygenase system, which eliminates the need for microsomal supplement. This test system is comparable to the Ames test and the sister-chromatid exchange test in sensitivity for measuring chromosome damage. (38 Refs)

43. MUTAGENICITY OF N-HYDROXY-2-ACETYLAMINOFLUORENE AND N-HYDROXYPHENACETIN AND THEIR RESPECTIVE DEACETYLATED METABOLITES IN NITROREDUCTASE DEFICIENT SALMONELLA TA98FR AND TA100FR.

Wirth PJ, Alewood P, Calder I, Thorgeirsson SS
Biochemical Pharmacology Section, Lab. Chemical Pharmacology, NCI, NIH, Bethesda, MD, 20205
Carcinogenesis; 3(2):167-170 1982

The mutagenicity of N-hydroxy-2-acetylaminofluorene and N-hydroxyphenacetin and their respective deacetylated metabolites, N-hydroxy-2-aminofluorene and 2-nitrosofluorene, and N-hydroxyphenetidine and p-nitrosophenetole was determined in nitroreductase deficient Salmonella tester strains TA98FR and TA100FR. The mutagenicity of N-hydroxy-2-acetylaminofluorene mediated by either rat liver microsomes or rat liver 105,000 g supernatant fractions was no different in either TA98 (nitroreductase proficient) or TA98FR (nitroreductase deficient). Similarly the mutagenicity of N-hydroxyphenacetin mediated by hamster liver microsomes was not affected by either the presence or absence of nitroreductase activity in TA100. N-Hydroxy-2-aminofluorene and 2-nitrosofluorene were equipotent direct acting mutagens in both TA98 and TA98FR, as were both N-hydroxyphenetidine and p-nitrosophenetole in TA100 and TA100FR. Ascorbate (5 mM) and NADPH (1 mM) had no significant effect on the mutagenicity of either N-hydroxy-2-acetylaminofluorene, N-hydroxy-2-aminofluorene, or 2-nitrosofluorene in TA98 or TA98FR whereas ascorbate and NADPH markedly inhibited the mutagenicity of both N-hydroxyphenetidine and p-nitrosophenetole in both TA100 and TA100FR. Ascorbate appears to be inhibiting the mutagenicity of N-hydroxyphenetidine and p-nitrosophenetole as a result of the nonenzymatic chemical reduction of these compounds to non-mutagenic derivatives. (Author abstract) (15 Refs)

44. PHOTOPRODUCT FORMATION AND REPAIR CAPACITY IN A MUTANT OF BACILLUS CEREUS 569 PRODUCING UV-SENSITIVE SPORES.

Weinberger S, Evenchik Z, Hertman I
Israel Inst. Biological Res., Ness Ziona, Israel
Mutat Res; 94(1):1-12 1982

The isolation of N-methyl-N'-nitro-N-nitroso-guanidine-induced mutants of Bacillus cereus 569 sensitive to UV in both vegetative and sporal stages is reported. In this mutant (2422) a single mutation in a gene coding for a step in excision repair apparently leads to the observed sensitivity of both cells and spores. Dipicolinic acid content of spores of strain 2422 was similar to that of wild type, indicating that the mutation induced was not involved in the synthesis of this product. For a given UV dose, both the mutant 2422 and the wild type

formed the same types and the same amount of photoproducts. The dominant photoproduct for vegetative cells was cyclobutane-thymine dimers, and for spores 5-thyminyl-5,6-dihydrothymine (TDHT). Under conditions permitting germination but no outgrowth, only about 50% of TDHT lesions were removed; no significant difference was observed in rates of removal in the wild type vs the mutant strain. Under growing conditions only the wild-type 569 improved in rate of removal of TDHT. These findings suggest more than one pathway for TDHT removal. Under growing conditions plus energy source, the wild type 569 excised approx 75% of initial thymine dimers, compared to only 26% in the mutant. Reversion analysis indicated that UV resistance was regained by single gene mutation. This gene is apparently involved in the removal of bases or nucleotides, and plays a major role in the repair of UV-induced damage in both spores and vegetative cells. (29 Refs)

45. RADIATION EQUIVALENCE OF GENOTOXIC CHEMICALS. VALIDATION IN CULTURED MAMMALIAN CELL LINES.

Murthy MS
Div. Radiological Protection, Bhabha Atomic Res. Center, Trombay, Bombay-400 085, India
Mutat Res; 94(1):189-197 1982

Radiation-equivalent chemical (REC) values were computed for the monofunctional alkylating agents ethylmethanesulfonate (EMS), methylmethanesulfonate (MMS), N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), ethylnitrosurea (ENU), and methylnitrosourea (MNU). REC values were calculated from published data as the ratio of the mutation frequency per unit dose of ionizing radiation to that of the alkylating agent. Mutation frequency data from different sources for a given cell line and locus were pooled and the mean taken. REC values were found to decrease in the order: nitrosoguanidine greater than nitrosourea greater than methylsulphonic esters. REC values for methylating agents were less than for corresponding ethylating agents. REC values for a given alkylating agent were not dependent upon cell line or locus, and fell within a narrow range for the rodent cell lines considered. Mutation frequency was expressed as the number of induced mutations/survivor/unit dose; for chemicals the unit was molar x hr (Mh). These values for the alkylating agents were: 1.28-5.49 x 10(-6) Mh for EMS; 3.57-14.30 x 10(-7) Mh for MMS; 2.60-3.90 x 10(-8) Mh for ENU; 7.50-17.81 x 10(-9) Mh for MNU; 7.36-13.89 x 10(-10) Mh for ENNG; and 4.27-32.50 x 10(-11) Mh for MNNG. These results validate the REC concept in mammalian cells, including human cells. (37 Refs)

CELLULAR EFFECTS OF NITROSO COMPOUNDS

46. DNA PRECURSOR POOL: A SIGNIFICANT TARGET FOR N-METHYL-N-NITROSOUREA IN C3H/10T1/2 CLONE 8 CELLS.

Topal MD, Baker MS
Dept. Pathology, Cancer Res. Center, Univ. North Carolina Medical Sch., Chapel Hill, NC, 27514
Proc Natl Acad Sci USA; 79(7):2211-2215 1982

Synchronized C3H/10T1/2 clone 8 cells were treated in vitro with a nontoxic dose of N-methyl-N-nitrosourea during their S phase. Chromatographic isolation of the deoxyribonucleotide DNA precursor pool and measurement of the precursor content per cell showed that a nucleic acid residue in the precursor pool is 190-13,000 times more susceptible to methylation than a residue in the DNA duplex, depending on the site of methylation. This conclusion comes from measurements indicating that, for example, the N-1 position of adenine in dATP is 6.3 times more methylated than the same position in the DNA, even though the adenine content of the pool is only a fraction (0.0005) of the adenine content of the DNA helix. The comparative susceptibility between pool and DNA was found to vary with the site of methylation in the order the N-1 position of adenine greater than phosphate greater than the N-3 position of adenine greater than the O6 position of guanine greater than the N-7 position of guanine. The significance of these results for chemical mutagenesis and carcinogenesis is discussed. (Author abstract) (25 Refs)

47. ENHANCEMENT OF NITROSOUREA CYTOTOXICITY IN VITRO USING HYDROCORTISONE.

Tew KD, Wang AL, Lindner DJ, Schein PS
Div. Medical Oncology, Lombardi Cancer Center, Georgetown Univ., Washington, DC, 20007
Biochem Pharmacol; 31(6):1179-1180 1982

Colony forming potential (CFP) of HeLa cells following treatment with various concentrations of 2-[3-(2-chloroethyl)-3-nitrosoureido]-D-glucopyranose (CLZ) or 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), with or without hydrocortisone-21-sodium succinate (HC) treatment is presented. CCNU was more toxic than CLZ, with all cells dead at 50 uM, irrespective of steroid pretreatment. The combination of HC pretreatment and CCNU decreased survival and CFP from 40% to 18% of control at 10 uM and 27% to 7% at 25 uM. The combination of CLZ and HC pretreatment produced enhanced cytotoxicity over CLZ alone at all concentrations of drug. Simultaneous administration of 10 uM HC with either nitrosourea resulted in an enhanced cell survival with CCNU and did not affect the cytotoxicity of CLZ. Thus, the scheduling was critical to cytotoxicity, with synergistic effects occurring only following HC priming. CLZ alkylation and carbamoylation into transcriptionally active chromatin could be linked to a disaggregation and overt relaxation of chromatin superstructure within the nucleus. This relaxation resulted in nuclear swelling, presumably mediated through nuclear matrix steroid receptors, which could function by altering the dynamic structural properties of the non-histone acidic protein scaffold of the nucleus. Presented data suggest that one or both of the nuclear targets (transcriptional chromatin and the nuclear matrix) may be important in determining the site-specific cytotoxic properties of nuclear reactant drugs such as nitrosoureas. (5 Refs)

48. ULTRASTRUCTURAL DIFFERENCES BETWEEN CONTROL AND NITROSOMETHYLUREA-TRANSFORMED CELLS OF RAT HEPATOCYTE ORIGIN.

Kaplan AE, Yamaguchi MK, Tralka TS, Hanna CH
NIH, Building 37-3B27, Bethesda, MD, 20208
Exp Cell Res; 138(2):251-260 1982

Ultrastructural comparisons identify significant differences between a control cell, TRL 12-13, and a nitrosomethylurea-transformed cell line, NMU-3, which secretes lactic acid in vitro and produces carcinomas in vivo. Both cell lines were established from rat hepatocytes. The NMU-3 cells show a marked reduction in mitochondria, both at confluence and at 48 hr post-confluence. This deficiency supports previous biochemical findings of altered bioenergetic pathways in the

NMU-3 cells, leading to increased output of lactic acid. In addition to deficiencies in mitochondria, the NMU-3 cells show a marked reduction in other membranous structures, including rough endoplasmic reticulum, Golgi apparatus, pinocytotic and coated vesicles. Polyribosome distribution at confluence and 48 hr later suggests that the transformed cells continue to synthesize intracellular protein, whereas the control cells appear to secrete protein for export at this time. (Author abstract) (29 Refs)

49. EFFECTS OF ALKYLATING AGENTS ON THE DNA REPLICATION OF CULTURED YOSHIDA SARCOMA CELLS.

Van Der Steen J, Van Wichen BH, Benckhuysen C
Div. Experimental Chemotherapy and Radiotherapy, Antoni Van Leeuwenhoek-Huis, The Netherlands Cancer Inst., Amsterdam, The Netherlands
Chem Biol Interact; 39(2):191-204 1982

Logarithmically growing Yoshida sarcoma cells were treated for 1 hr with low (2 decades cell kill) or high (more than 6 decades cell kill) doses of alkylating agent. Pulse and chase labeled DNA from treated cells were studied by alkaline sucrose gradient centrifugation. Nitrogen mustard (HN-2), 4-hydroperoxycyclophosphamide (CY-OOH), melphalan (L-PAM) and chlorambucil (CA) had no effect on the elongation rate of newly replicated DNA, both at low and high doses, although per cell the rate of DNA synthesis declined as inferred from the rates of [3H]thymidine incorporation compared to the increase in numbers of S phase cells in the treated populations. It is concluded that these drugs act specifically on the initiation step of the DNA replication, leaving chain elongation undisturbed. At low doses the chemically related sulfur mustard (SM) had also no effect on the maturation of new DNA but at high doses a decreased elongation rate was observed. A transient inhibition of chain growth was observed following treatment with a low dose of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). In contrast, the intercalating agent adriamycin showed a severe but delayed effect resulting in an almost complete block of the maturation. (Author abstract) (24 Refs)

50. IDENTIFICATION OF A PHOSPHOPROTEIN SPECIFICALLY INDUCED BY THE TRANSFORMING DNA OF RAT NEUROBLASTOMAS.

Padhy LC, Shih C, Cowing D, Finkelstein R, Weinberg RA
Center Cancer Res., Cambridge, MA, 02139
Cell; 28(4):865-871 1982

DNAs from nitrosoethylurea-induced rat neuroblastomas transform NIH/3T3 mouse fibroblasts in a transfection assay. DNAs of such transformed cells can be used in a subsequent cycle of transfection to generate secondary foci that contain virtually no foreign genetic material besides the sequences carrying the rat neuroblastoma transforming function. These secondary neuroblastoma transfectants were injected into young mice and grew out into fibrosarcomas. Sera from these mice were examined for reactivity with any proteins which were induced specifically by the neuroblastoma transforming sequence. These sera precipitate a polypeptide of about 185,000 daltons from 35S-methionine-labeled cell lysates of the rat neuroblastoma cells that served as DNA donors and in all transfection-derived primary and secondary foci. This protein is present in high levels in all neuroblastoma transfectant clones, but was not detectable in a variety of other transformed cells. Antisera were prepared from mice bearing tumors induced by transformed cells derived by transfection of DNAs from various tumor cell types unrelated to rat neuroblastoma. These antisera failed to immunoprecipitate the 185,000 dalton protein. These data indicate that the synthesis of the 185,000 dalton protein is specifically induced by the neuroblastoma transforming sequence. The protein may be encoded by the transforming sequence and may mediate transformation in this chemically induced tumor. (Author abstract) (9 Refs)

51. POLY(ADENOSINEDIPHOSPHORIBOSE) POLYMERASE INHIBITORS STIMULATE UNSCHEDULED DEOXYRIBONUCLEIC ACID SYNTHESIS IN NORMAL HUMAN LYMPHOCYTES.

Sims JL, Sikorski GW, Catino DM, Berger SJ, Berger NA
(c/o N. A. Berger) Hematology/Oncology Div., Dept. Medicine, Washington Univ. Sch. Medicine, St. Louis, MO, 63110
Biochemistry; 21(8):1813-1821 1982

Thirty-three analogues of the nicotinamide and adenine portions of NAD+ were evaluated for (1) their effectiveness as inhibitors of poly(adenosinediphosphoribose) polymerase in nucleotide permeable lymphocytes, (2) their ability to interfere with NAD+ lowering in DNA-damaged cells, (3) their ability to inhibit accumulation of poly(adenosinediphosphoribose) in DNA-damaged cells, and (4) their ability to stimulate unscheduled DNA synthesis in DNA-damaged cells. Poly(adenosinediphosphoribose) polymerase was effectively inhibited by six-membered aromatic ring compounds containing a carboxamide group such as nicotinamide, picolinamide, 5-methylnicotinamide, benzamide, 3-aminobenzamide, and 5-methoxybenzamide. Compounds containing a carboxylic acid group rather than a carboxamide group did not inhibit poly(adenosinediphosphoribose) polymerase. Purine analogues such as theobromine and theophylline were also effective inhibitors of poly(adenosinediphosphoribose) polymerase. The ability of these compounds to inhibit poly(adenosinediphosphoribose) polymerase in nucleotide permeable cells correlated with their ability to retard NAD+ lowering in vivo in cells treated with N-methyl-N'-nitro-N-nitrosoguanidine. However, the most effective polymerase inhibitors caused the greatest retardation in the rate of NAD+ lowering. The compounds that were the most effective polymerase inhibitors in vitro were also the most potent in retarding NAD+ lowering in vivo and the most potent in delaying poly(adenosinediphosphoribose) accumulation in vivo. These compounds were also found to be the most effective stimulators of unscheduled DNA synthesis. For example, unscheduled DNA synthesis in UV-irradiated cells was stimulated two-fold by treatment with 2 mM benzamide, nicotinamide, or 3-aminobenzamide. (24 Refs)

52. ENHANCEMENT OF ULTRAVIOLET OR N-METHYL-N'-NITRO-N-NITROSOGUANIDINE SENSITIVITY OF DICTYOSTELIUM DISCOIDEUM BY 3-AMINOBENZAMIDE.

Ohnishi T, Eimoto H, Okaichi K
Molecular and Cell Biology Program, 201 Althous Lab., Pennsylvania State Univ., University Park, PA, 16802
Photochem Photobiol; 35(4):515-519 1982

The amoeboid cells of Dictyostelium discoideum NC-4 possess a 3-aminobenzamide(3-ABA)-sensitive repair mechanism for DNA damages induced by UV-irradiation or N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-treatment. We have studied the effect of 3-ABA on each step of excision repair in the UV-irradiated cells. Although the nicking of DNA-strand and the excision of pyrimidine dimers are insensitive to 3-ABA, the rejoining of DNA strand-breaks is sensitive. The frequency of

mutation induced by UV-irradiation or MNNG-treatment is depressed by 3-ABA. The mechanisms of repair inhibition by 3-ABA are discussed. (Author abstract) (24 Refs)

53. MORPHOLOGIC TRANSFORMATION AND CHROMOSOMAL CHANGES INDUCED BY CHEMICAL CARCINOGENS IN SKIN FIBROBLASTS FROM PATIENTS WITH FAMILIAL ADENOMATOSIS COLI.

Miyaki M, Akamatsu N, Ono T, Tonomura A, Utsunomiya J
Dept. Biochemistry, Tokyo Metropolitan Inst. Medical Science, 3-18-22 Honkomagome, Bunkyoku, Tokyo 113, Japan
JNCI; 68(4):563-571 1982

Skin fibroblasts from patients with familial adenomatosis coli (AC) and normal individuals were treated once with the carcinogen 4-nitroquinoline 1-oxide or N-methyl-N'-nitro-N-nitrosoguanidine and then passaged sequentially. Morphologically altered cells appeared in the cultures of carcinogen-treated AC fibroblasts at passages 6-8 (days 100-140) after treatment with the carcinogens, but carcinogen-treated normal cells and untreated AC and normal cells did not become altered even after cultivation for 25 passages. The cultures containing morphologically altered cells showed characteristics of transformed cells, such as a high frequency of colony formation in soft agarose, increased growth ability, and chromosomal abnormalities. The results suggest that AC patients have increased susceptibility to morphologic transformation and chromosomal changes induced by chemical carcinogens. (Author abstract) (19 Refs)

IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS

54. SEROLOGIC ANALYSIS OF NITROSOUREA-INDUCED RAT GLIOMAS.

Pfreundschuh M, Cravioto H, Hochwald G, Ransohoff J
Lab. Neuropathology, Dept. Pathology, Sch. Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016
JNCI; 68(3):501-505 1982

Inbred CDF rats (cesarean-delivered F344 rats) were immunized with either a nitrosourea-induced glioma EA-285 or its subline EA-285A and both with and without Corynebacterium parvum. A humoral immune response in syngeneic rats to the immunizing tumor was demonstrated with micromodifications of different rosette assays (immune adherence assay, protein-A assay, and anti-C3-mixed hemadsorption assay). Extensive absorption studies of two immune sera with the highest reactivity revealed two glioma-specific antigens (or 2 components of 1 antigen) on the cell surface of the cloned tumor subline. One antigen was present only on the cell surface of the subline of the glioma used for both immunization and absorption analyses. The other antigen appeared on the cell surface of both the cloned subline EA-285A and the parental cell line EA-285. These preliminary studies showed that CDF rats immunized against a syngeneic glioma mounted a humoral immune response that appeared to be individually tumor-specific. (Author abstract) (21 Refs)

55. CHARACTERIZATION OF AN RNA-DIRECTED DNA POLYMERASE FROM MOUSE SPLEEN INFECTED WITH LEUKAEMIA VIRUS ACTIVATED DURING N-METHYL-N-NITROSO UREA-INDUCED LEUKAEMOGENESIS.

Drescher B, Ehm I, Fey F
Central Inst. Molecular Biology, Acad. Sciences of German Democratic Republic, DDR-115 Berlin-Buch, E. Germany
Acta Virol (Praha); 26(1/2):41-49 1982

An RNA-directed DNA polymerase was purified from mouse spleen infected with leukemia virus activated during N-methyl-N-nitroso urea- (MNU-) induced leukemogenesis. The enzyme was isolated from the microsomal fraction and purified by successive chromatography on Sephadex G-200 and phosphocellulose. Estimation of mol wt from the sedimentation rate of the purified enzyme in a sucrose gradient gave a value of 70,000. The enzyme had a pH optimum of 7.4, a KCl optimum of 50 mmol/l, an Mn++ optimum of 0.2 mmol/l, and a temperature optimum of 25 C, when (rA)n - (dT)10 was used as the template-primer. It preferred (rA)n - (dT)10 as the template-primer and transcribed (rC)n - (dG)12 and (OMeC)n - (dG)12. A comparison of the properties of this DNA polymerase with the enzyme purified from murine Type C retroviruses showed that the MNU-activated virus enzyme was both biochemically and biophysically indistinguishable from murine leukemia virus DNA polymerases. (Author abstract) (18 Refs)

56. ISOLATION AND PRELIMINARY CHARACTERIZATION OF A PHOSPHONOACETIC ACID-RESISTANT AND TEMPERATURE-SENSITIVE MUTANT OF HERPES SIMPLEX VIRUS TYPE I.

Daksis JI, Priemer MM, Chan VL
Dept. Microbiology and Parasitology, Univ. Toronto, Toronto, Ontario M5S 1A1, Canada
J Virol; 42(1):20-29 1982

A group of 43 phosphonoacetic acid (PAA)-resistant mutants of herpes simplex virus Type 1 was isolated after the mutagenesis of infected cells with nitrosoguanidine. One of these mutants, designated PAA1rts1, was found to be temperature sensitive (ts), that is, unable to replicate at 39.5 C, the nonpermissive temperature. Recombination analysis of PAA1rts1 indicated that the PAA1r mutation and the ts1 mutation are loosely linked and are located on two separate genes. PAA1rts1 showed a defect in viral DNA synthesis at 39.5 C, which presumably can be attributed to the production of a PAA-resistant and thermolabile DNA polymerase. PAA1rts1 was also defective in the shutoff of host DNA synthesis at the restrictive temperature. (Author abstract) (20 Refs)

EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS

57. CHEMICALS, CANCER, AND CYTOCHROME P-450.

Alexander LS, Goff HM
Univ. Iowa, Iowa City, IA, 52242
J Chem Educ; 59(3):179-182 1982

Cytochrome P450 (P450) and related monooxygenases mediate a variety of complex chemical reactions, including the processing of many foreign chemical substances in the circula-

tion. Nearly all putative carcinogens (except for the nitrosamides and a few alkylating agents) require enzymatic activation before they can induce neoplastic transformation of normal cells. The ultimate carcinogen is an electrophile, which covalently binds to DNA, RNA, protein chains, and/or other molecules of importance to cellular reproduction. P450 is often involved in the involved in the metabolic activation of carcinogens. Available evidence on the role of P450 in detoxification and carcinogen activation, its hypothetical reaction cycle with substrates, and the important chemical models used in delineate its active site structure are discussed. (32 Refs)

58. RELATIONSHIP BETWEEN VITAMIN E AND CANCER - FACTS, NOT FANCY.

Ellison NM
Dept. Medical Oncology, Geisinger Medical Center, Danville, PA
Cancer Bull; 34(1):43-44 1982

The roles of vitamin E in inhibition of carcinogenesis and amelioration of conventional cancer treatment toxicity are discussed. Studies with mammalian models suggest that vitamin E may act as a protector against radiation-induced cellular damage and as a radiosensitizer in cancer treatment. The conflict between these antagonistic functions must be resolved. Vitamin E has been shown to ameliorate the toxic effects of doxorubicin in animal models without adversely affecting antineoplastic activity. Vitamin E may also act as an inhibitor of stomach cancer by inhibiting the reactions converting nitrites and nitrates to nitrosourea; possible prevention of gastric cancer by steady consumption of vitamin E and C has been suggested. Vitamin E, an antioxidant with the ability to inhibit free-radical-induced lipid peroxidation, may have some role in human carcinogenesis and cancer treatment, but evidence to support such a role is insufficient. (16 Refs)

59. N-NITROSAMINES IN THE BEER AND CERTAIN SOFT DRINKS.

Zhukova GF, Somina SI, Ipatova GP, Medvedev FA, Bershova TM
Inst. Nutrition, Moscow, USSR
Vopr Pitan; (1):48-50 1982

The content of carcinogenic N-nitrosamines was studied in samples of beer and different soft drinks. Sensitive fluorescence and chromatographic mass spectrum analysis showed only the traces of diethylnitrosamine in all samples tested. (8 Refs) (In RUS)

U. S. GOVERNMENT PRINTING OFFICE : 1992—361-547/[illegible]

AUTHOR INDEX WITH CITATION NUMBERS

Abe S. 35
Akamatsu N. 53
Alewood P. 43
Alexander LS. 57
Appel KE. 8
Au W. 36
Azari MR. 9
Baker MS. 46
Benckhuysen C. 49
Berger NA. 51
Berger SJ. 51
Bershova TM. 59
Bertram B. 6
Borgna JL. 2
Calder I. 43
Cameron RG. 17
Catino DM. 51
Chan VL. 56
Chandrasekaran. 29
Chavis C. 2
Chopra P. 18
Clark A. 1
Cohen BI. 28
Coombes RC. 13
Cowing D. 50
Cravioto H. 54
Daksis JI. 56
De Gourcy C. 2
Deschner EE. 28
Dhar A. 18
Drescher B. 55
Dunn WJ. 10
Ehm I. 55
Eimoto H. 52
Eisenbrand G. 4
Ellison NM. 58
Enomoto K. 16
Evenchik Z. 44
Evensen G. 40
Fabricant JD. 36
Fabricant RN. 36
Farber E. 16
Farrelly JG. 3
Feron VJ. 33
Fey F. 55
Finkelstein R. 50
Fiszer-Szafarz. 22
Fox J. 1
Fukushima S. 25
Gabrial GN. 31
Gersel A. 24
Glebov AV. 21
Goff HM. 57
Gold B. 23
Graf H. 8
Guion CW. 27
Gusterson BA. 13
Guttenplan JB. 34
Hagiwara A. 25
Hanna CH. 48
Hansen HH. 24
Hemminki K. 5
Herren SL. 27
Hertman I. 44
Hirsch FR. 24
Hjelmgren T. 39
Hochwald G. 54
Imaida K. 17
Imbach JL. 2
Ioannides C. 7
Ipatova GP. 59
Ito N. 17
Ito N. 25
Janzowski C. 4
Jap P. 12
Kaplan AE. 48
Karran P. 39
Karran P. 41
King DJ. 9
Knazek RA. 30
Kocan RM. 42
Kruysse A. 33
Landolt ML. 42
Lawson TA. 20
Lijinsky W. 11
Lijinsky W. 3
Lindahl T. 39
Lindner DJ. 47
Lintas C. 1
Liu SC. 30
Lombardi B. 26
Marinus MG. 41
Matsumoto M. 14
McCormick DL. 32
Medvedev FA. 59
Miller SB. 15
Milmore JE. 29
Milstein S. 34
Miyaki M. 53
Monaghan P. 19
Moon RC. 32
Morgan KS. 36
Murthy MS. 45
Nagasawa S. 14
Nakanishi K. 25
Nayak NC. 18
Newberne PM. 1
Newberne PM. 31
Nissen NI. 24
Ohnishi T. 52
Okaichi K. 52
Ono T. 53
Padhy LC. 50
Parke DV. 7
Pereira MA. 27
Pfreundschuh M. 54
Phillipson CE. 7
Pool BL. 4
Pretlow TG. 15
Pretlow TP. 15
Preussmann R. 4
Priemer MM. 56
Raicht RF. 28
Ransohoff J. 54
Reuber MD. 11
Ritter MA. 19
Ross AE. 20
Rudenko L. 37
Rudland PS. 19
Saavedra JE. 11
Saavedra JE. 3
Sabo KM. 42
Salmasi S. 23
Sasaki M. 35
Savage RE. 27
Schaffer R. 6
Schein PS. 47
Schrager TF. 31
Scott JA. 15
Seeberg E. 40
Seiki Y. 14
Seits IF. 21
Shibata I. 14
Shih C. 50
Shinozuka H. 26
Sikorski GW. 51
Sims JL. 51
Singer SS. 11
Sivak A. 37
Somina SI. 59
Stewart ML. 3
Takahashi S. 26
Takezawa J. 14
Tamano S. 25
Tannenbaum SR. 1
Teague LG. 37
Tew KD. 47
Thorgeirsson SS. 43
Tonomura A. 53
Topal MD. 46
Tralka TS. 48
Tsuda H. 17
Utsunomiya J. 53
Van Der Steen J. 49
Van Wichen BH. 49
Van de Molengra. 12
Vindelov LL. 24
Vooijs P. 12
Wang AL. 47
Warburton MJ. 19
Weinberg RA. 50
Weinberger S. 44
Weisburger JH. 29
Williams JC. 13
Wirth PJ. 43
Wirtz P. 12
Wiseman A. 9
Wold S. 10
Woutersen RA. 33
Yamaguchi MK. 48
Zhukova GF. 59
Zimmering S. 38

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICITY AND METABOLISM OF ACRYLONITRILE.
Sapota A, Chmielnicka J
Zaklad Metabolizmu Substancji Toksycznych, Instytut Medycyny Pracy, ul. Teresy 8, 90-950 Lodz, Poland
Med Pr; 32(1):25-33 1981
In POL

2. A REVIEW OF THE GENOTOXICITY OF FOOD, DRUG AND COSMETIC COLOURS AND OTHER AZO, TRIPHENYLMETHANE AND XANTHENE DYES.
Combes RD, Haveland-Smith RB
Dept. Biological Sciences, Portsmouth Polytechnic, King Henry I St., Portsmouth, PO1 2DY, Hants, England
Mutat Res; 98(2):101-248 1982

3. CARCINOGENICITY OF AIRBORNE FINE PARTICULATE BENZO(A)PYRENE: AN APPRAISAL OF THE EVIDENCE AND THE NEED FOR CONTROL.
Perera F
Natl. Resources Defense Council, Inc., 122 East 42nd St., New York, NY, 10168
Environ Health Perspect; 42:163-185 1981

4. TOXICOLOGY OF N-NITROSO COMPOUNDS.
Coulston F, Olajos EJ
Albany Medical Coll., Albany, NY, 12208
Ecotoxicol Environ Saf; 6(1):89-96 1982

5. CRITICAL REVIEW OF THE MUTAGENIC AND OTHER GENOTOXIC EFFECTS OF DIRECT COAL LIQUEFACTION.
Kimball RF, Munro NB
Oak Ridge Natl. Lab., Oak Ridge, TN
Critical Review of the Mutagenic and Other Genotoxic Effects of Direct Coal Liquefaction. Available from National Technical Information Service, Springfield, VA, as DE81027859:, 216 pp., 1981.

6. CARCINOGENICITY AND ITS EFFECT ON MEDICINAL RESEARCH PROGRAMS IN THE USA.
Van Ryzin RJ
Pharmaceutical Res. and Development, Sandoz, Inc., East Hanover, NJ, 07936
Med Res Rev; 2(2):153-166 1982

7. ANTIPROTOZOAL DRUGS (SIDE EFFECTS).
Nir I
Dept. Pharmacology and Experimental Therapeutics, The Hebrew Univ., Hadassah Medical Sch., Jerusalem, Israel
Side Eff Drugs Annu; (5):278-284 1981

8. DRUGS USED IN TUBERCULOSIS AND LEPROSY (SIDE EFFECTS).
Elis J
Inst. Pharmacology, Czechoslovak Acad. Sciences, Albertov 4, Prague 2, Czechoslovakia
Side Eff Drugs Annu; (5):290-297 1981

9. SEX HORMONES AND RELATED COMPOUNDS, INCLUDING ORAL CONTRACEPTIVES.
Plotz EJ, Nocke W, Schander K, Patt V, Kaulhausen H
Dept. Obstetrics and Gynecology, Univ. Bonn, 5300 Bonn Venusberg, W. Germany
Side Eff Drug Annu; (5):358-380 1981

RADIATION CARCINOGENESIS

10. NEPTUNIUM - THE NEGLECTED ACTINIDE: A REVIEW OF THE BIOLOGICAL AND ENVIRONMENTAL LITERATURE.
Thompson RC
Biology Dept., Pacific Northwest Lab., Richland, WA, 99352
Radiat Res; 90(1):1-32 1982

11. CARCINOGENIC EFFECT OF RADIOACTIVE PRODUCTS.
Vasilenko Ila
No affiliation given
Vopr Onkol; 28(1):76-83 1982
In RUS

DIETARY FACTORS IN CARCINOGENESIS

12. FIBRES, NUTRITION AND THE GUT.
Schrijver M, Tytgat GN
Dept. Internal Medicine, Div. Gastroenterology, Univ. Amsterdam, 1 e Helmerstraat 104, 1054 EG Amsterdam, The Netherlands
Neth J Med; 25(2):49-55 1982

13. DIETARY FIBER AND DISEASE.
Kritchevsky D
Wistar Inst. Anatomy and Biology, Philadelphia, PA
Bull NY Acad Med; 58(3):230-241 1982

14. ASSESSING HUMAN EPIDEMIOLOGIC DATA ON DIET AS AN ETIOLOGIC FACTOR IN CANCER DEVELOPMENT.
Enstrom JE
Sch. Public Health, Univ. California, Los Angeles, CA
Bull NY Acad Med; 58(3):313-322 1982

15. NUTRITION AND CANCER: MECHANISMS OF GENOTOXIC AND EPIGENETIC CARCINOGENS IN NUTRITIONAL CARCINOGENESIS.
Weisburger JH, Horn C
American Health Foundation, Valhalla, NY, 10595
Bull NY Acad Med; 58(3):296-312 1982

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

16. THE AH LOCUS, A MULTIGENE FAMILY NECESSARY FOR SURVIVAL IN A CHEMICALLY ADVERSE ENVIRONMENT: COMPARISON WITH THE IMMUNE SYSTEM.
Nebert DW
Developmental Pharmacology Branch, National Inst. Child Health, NIH, Bethesda, MD, 20205
Adv Genet; 21:1-52 1982

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

17. SKIN CANCER: OCCUPATIONAL CAUSES.
Bickers DR
Dept. Dermatology, Case Western Reserve Univ., Cleveland, OH
Consultant; 22(4):392-393,397,400-401 1982

18. OCCUPATIONAL AND ENVIRONMENTAL HEALTH PROBLEMS OF THE DEVELOPING OIL SHALE INDUSTRY: A REVIEW.
Rom WN, Lee JS, Craft BF
Rocky Mountain Center Occupational and Environmental Health, Dept. Internal Medicine, Family and Community Medicine, Univ. Utah Sch. Medicine, Bldg. 512, Salt Lake City, UT, 84112
Am J Industr Med; 2(3):247-260 1981

19. POLYCYCLIC AROMATIC HYDROCARBONS IN THE OCCUPATIONAL ENVIRONMENT: WITH SPECIAL REFERENCE TO BENZO[A]PYRENE MEASUREMENTS IN SWEDISH INDUSTRY.
Lindstedt G, Sollenberg J
Chemistry Dept., Natl. Board Occupational Safety and Health, S-171 84 Solna, Sweden
Scand J Work Environ Health; 8(1):1-19 1982

20. GENETIC RISKS AND ENVIRONMENTAL SURVEILLANCE: EPIDEMIOLOGICAL ASPECTS OF MONITORING INDUSTRIAL POPULATIONS FOR ENVIRONMENTAL MUTAGENS.
Buffler PA, Aase JM
Sch. Public Health, Univ. Texas Health Science Center at Houston, P.O. Box 20186, Houston, TX, 77025
JOM; 24(4):305-314 1982

21. OSHA AT THE THRESHOLD: SETTING PERMISSIBLE EXPOSURE LEVELS FOR KNOWN CARCINOGENS AFTER AMERICAN PETROLEUM INSTITUTE.
Blackmar GB
No affiliation given
San Diego Law Rev; 18(4/5):633-661 1981

22. CARCINOGENESIS: PROBLEMS AND PARADOXES. THE 1981 GEORGE H. GEHRMANN LECTURE.
Kotin P
4505 South Yosemite, 339, Denver, CO, 80237
JOM; 24(4):290-294 1982

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

23. MODIFICATIONS OF CHROMATIN STRUCTURE IN CONTROL OF GENE EXPRESSION.
Hull LA
104 Depot St., New Sharon, IA, 50207
Med Hypotheses; 8(2):113-133 1982

24. PLASMINOGEN ACTIVATORS IN NEOPLASTIC CELLS.
Goloborod'ko OP, Veremeenko KN
A. I. Kolomiichenko Res. Inst. Otolaryngology, Kiev, USSR
Eksp Onkol; 4(1):3-7 1982
In RUS

25. TUMOR PROMOTION BY REGENERATIVE EPIDERMAL HYPERPLASIA IN MOUSE SKIN.
Argyris TS
Dept. Pathology, Upstate Medical Center, State Univ. New York, Syracuse, NY, 13210
J Cutan Pathol; 9(1):1-18 1982

26. SEX HORMONES AND LIVER CANCER.
Williams GM
Naylor Dana Inst. for Disease Prevention, New York Medical Coll., Valhalla, NY
Lab Invest; 46(3):352-354 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

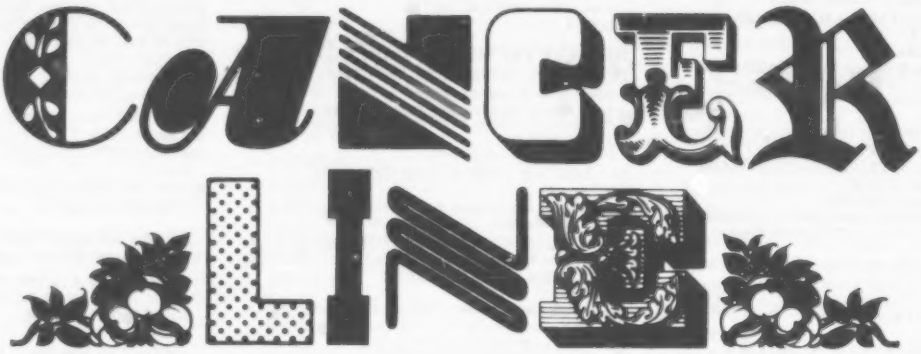
27. UTILIZATION OF CELL TRANSFORMATION TESTS IN THE DETECTION OF CHEMICAL CARCINOGENS.
Elias Z, Cavelier C
Institut National de Recherche, Centre de Recherche de Nancy, avenue de Bourgogne, F-54500 Vandoeuvre-les-Nancy, France
Bull Cancer (Paris); 69(1):33-57 1982
In FRE

28. FAILURES AND CRITIQUE OF THE BEIR III LUNG CANCER RISK ESTIMATES.
Cohen BL
Univ. Pittsburgh, Pittsburgh, PA, 15260
Health Phys; 42(3):267-284 1982

OTHER REVIEWS IN CARCINOGENESIS

29. CANCER. AN INTRODUCTION.
Creasey WA
Dept. Pharmacology, Univ. Pennsylvania Sch. Medicine, Philadelphia, PA
Cancer. An Introduction. New York, Oxford University Press, 271 pp., 1981.

30. CANCER 1980: ACHIEVEMENTS, CHALLENGES, AND PROSPECTS.
Clark RL
Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer; 49(9):1739-1745 1982



More Than Just A Fancy Name

Mention CANCERLINE to your librarian and the world's foremost collection of cancer information is at your disposal. With the help of this computerized data system, you can obtain information on the following:

Cancer Literature

The literature date base, **CANCERLIT**, allows you to survey more than 3,000 biomedical journals for information on your topic of interest. Your search will also alert you to meeting proceedings, monographs, and books published in that area. Informative abstracts averaging 200 words are provided with each citation.

Current Cancer Research

The data base **CANCERPROJ** allows you to retrieve descriptions of current work in any cancer research area. The descriptions, which state research objective, methodology, and experimental results, are supplied for projects underway in 77 countries around the world.

Cancer Therapy Protocols

The **CLINPROT** section of CANCERLINE is designed primarily for clinicians. It provides detailed summaries of currently active experimental protocols for any cancer site, agent, or type.

Ask your biomedical librarian about CANCERLINE.
CANCERLINE is sponsored by the International Cancer Research Data Bank—a program of the National Cancer Institute.

CANCERLINE

VIDEOTAPES

ON CURRENT TOPICS IN CANCER RESEARCH

A pilot project of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute

Three series are available . . .

THE RELATION OF CARCINOGEN ACTION ON DNA TO CELL TRANSFORMATION

PETER MAGEE Fels Research Institute	*Keynote Address*	#VK01 28 min.
JAMES K. SELKIRK Oak Ridge National Laboratories	*Metabolic Activation and Macromolecular Binding of Chemical Carcinogens*	#VK02 51 min.
PHILIP C. HANAWALT Stanford University	*Cellular Responses to Damaged DNA*	#VK03 54 min.
CHARLES HEIDELBERGER University of Southern California	*Mutagenesis and Oncogenic Transformation of Mouse Embryo Cells*	#VK04 54 min.
FRED RAPP Milton S. Hershey Medical Center	*The Interaction of Herpesviruses and Host Cells Leading to Latency or Transformation*	#VK05 52 min.
	Panel Discussion	#VK06 31 min.

MECHANISMS OF METASTASIS

ISAIAH FIDLER Frederick Cancer Research Center	*The Heterogeneous Nature of Cancer Metastasis and Implications for Therapy*	#VB01 47 min.
GEORGE POSTE Smith, Kline and French Laboratories	*Phenotypic Analysis of Metastatic Cell Populations*	#VB02 42 min.
LANCE LIOTTA National Cancer Institute	*Tumor Cell Invasion of Basement Membranes and Extracellular Matrices*	#VB03 33 min.
EVERETT SUGARBAKER Miami Cancer Institute	*Some Clinical Characteristics of Metastasis in Man*	#VB04 41 min.

AUTOMATED CYTOLOGY

Part One: Principles and Techniques	#VB05 56 min.
Part Two: Biological Applications	#VB06 52 min.

VIDEOTAPES ON CURRENT TOPICS IN CANCER RESEARCH are in the 3/4" U-matic format and can be played on video equipment which accepts the NTSC standard (the standard for videotapes produced in the U.S.). The two Automated Cytology tapes (#VB05 and #VB06) are also available in the PAL format.

The videotapes are available on a loan basis. If you would like to schedule viewing for your group, or for more information, please write to:

Videotape Coordinator
ICRDB Program
Westwood Building, Room 10A18
Bethesda, MD 20205

Please specify three choices for viewing dates, and the tapes desired.

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
5285 Port Royal Road
Springfield, Va. 22161

OFFICIAL BUSINESS

Penalty for Private Use, $300

PRINTED MATTER

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF COMMERCE
COM-211

THIRD CLASS
BULK RATE

U.S.MAIL

CK-01

CANCERGRAMS are distributed for the International Cancer Research Data Bank (ICRDB) by the National Technical Information Service (NTIS). **CANCERGRAMS** are available from NTIS on a standing order basis at $2 each for North American Continent addressees and $3 each for other addressees. An NTIS deposit account is required. For a list of subject categories or other information, please write to:

Subscription Section
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161

NOTICE OF MAILING CHANGE

☐ Check here if you wish to discontinue receiving this publication.

☐ Check here if your address has changed and you wish to continue receiving this publication. (Be sure to furnish your complete address including zip code.)

Tear off cover with address label still affixed and send to:

Computer Support Center
ICRDB Program
IIT Research Institute
10 West 35th Street
Chicago IL. 60616

CK 01/82/10

NCI/ICRDB/CK01 82/10

PB82-935110

NEWARK PUBLIC LIBRARY

NOV 15 1982

GOVT. PUBS. DEPOSITORY 376

ICRDB CANCERGRAM

CHEMICAL CARCINOGENESIS

Nitroso Compounds

SERIES CK01 No. 82/10

OCTOBER, 1982

This Cancergram is a service of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM of the U.S. National Cancer Institute. Every few weeks, an updated Cancergram containing abstracts of selected cancer-related articles recently published in more than 3000 journals, and dealing with the topic indicated by the above title, is sent to researchers working in this area. These researchers are identified on the basis of the description of their current research project that has been submitted to the ICRDB Program, directly or via granting agencies.

This Cancergram is prepared by the Cancer Information Dissemination and Analysis Center (CIDAC) for Carcinogenesis Information. ***If this Cancergram is useful and valuable, please send your comments to the CIDAC address below, since future editions depend on user satisfaction and user needs:***

CIDAC FOR CARCINOGENESIS INFORMATION
SCIENCE INFORMATION SERVICES
FRANKLIN INSTITUTE RESEARCH LABORATORIES
20TH AND RACE STREETS
PHILADELPHIA, PA 19103

In this issue:

- FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS..... 1-2
- METABOLISM OF NITROSO COMPOUNDS..... 3-17
- INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS..... 18-54
- MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS..... 55-72
- MUTAGENICITY OF NITROSO COMPOUNDS..... 73-75
- CELLULAR EFFECTS OF NITROSO COMPOUNDS..... 76-85
- IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS..... 86-88
- EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS..... 89-95
- REVIEWS INCLUDING NITROSO COMPOUNDS..... 96-106

FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS

1. THE EFFECTS OF ASCORBIC ACID AND SORBIC ACID ON N-NITROSAMINE FORMATION IN A HETEROGENEOUS MODEL SYSTEM.

Massey RC, Forsythe L, McWeeny DJ
Food Lab., Ministry Agriculture, Fisheries and Food, Haldin House, Queen St., Norwich NR2 4SX, England
J Sci Food Agric; 33(3):294-298 1982

The effects of ascorbic acid (AA) and sorbic acid (SA) as nitrite scavengers in a meat-simulating system of 20% non-aqueous solvent, 54% aqueous buffer, 18% protein, and 8% sodium carboxymethylcellulose were determined. Nitrosamines were analyzed by gas chromatography. Reactions were carried out at pH 5.25 for 50 hr at 37 C to ensure that detectable levels of nitrosamines were formed. Addition of decane to the reaction mixture increased N-nitrosodibutylamine (NDBA) formation four-fold compared to the mixture with glycerol tributyrate (GTB). With GTB, there was a four-fold increase in N-nitrosopyrrolidine (NPYR) formation, which was ascribed to greater pyrrolidine partitioning in this more polar non-aqueous

HE 20.3173/2:

phase. In the absence of decane both NDBA and NPYR formation were reduced by addition of AA, but with decane present AA had no major effect after 50 hr. When AA was replaced with SA, NPYR production was reduced 50% in the control aqueous system, as with AA, but a 50% reduction was also observed in the GTB system, evidently because of greater SA solubility in the non-aqueous phase. Situations that enhance amine solubility in the non-aqueous phase also enhance nitrosation, but the effect can be reduced by the use of an additive which is soluble in that phase. (14 Refs)

2. RADIOIMMUNOASSAYS FOR N'-NITROSONORNICOTINE AND N'-ACYLNORNICOTINE ANALOGS.

Castonguay A, Van Vunakis H
Div. Chemical Carcinogenesis, American Health Foundation, Valhalla, NY, 10595
Methods Enzymol; 84:641-650 1982

Production of antibodies and development of radioimmunoassays (RIA) for N'-nitrosonornicotine (NNN), N'-formylnornicotine, and N'-acetylnornicotine are described. The ability of NNN and various structurally related compounds to inhibit the binding of [2'-3H]NNN to the homologous antibody is reported. Fifty percent inhibition (I50) was achieved with 3.5 nanog NNN. Since the I50 substrate:I50 product ratio is greater than 10(3), small amounts of nitrosated product can be detected in a reaction mixture that contains relatively large amounts of substrate. Appropriately diluted samples were assayed directly. (41 Refs)

METABOLISM OF NITROSO COMPOUNDS

3. REACTIVE INTERMEDIATES FROM NITROSAMINES.

Archer MC
Dept. Medical Biophysics, Univ. Toronto, Toronto M4X 1K9, Canada
Adv Exp Med Biol; 136(partB):1027-1035 1982

Experiments with reactive intermediates from nitrosamines are reviewed. Rat liver fractions prepared from homogenate were incubated with 0.28 mole of N-nitrosodi-n-propylamine (NDPA) at 37 C. Microsomal metabolism of NDPA in vitro led to production of isopropanol and n-propanol through the intermediary of a carbocation. DNA obtained from livers of Sprague-Dawley rats previously injected ip with N-[2,3(3)-H]nitrosodi-n-propylamine was incubated with 7-n-propylguanine (7-nPG) and 7-isopropylguanine (7-iPG) and then hydrolyzed. Reverse phase chromatography showed that the DNA hydrolysate contained 7-nPG only, although a similar experiment demonstrated 7-iPG in rat liver RNA. N-nitroso-2-hydroxypropylpropylamine (NHPPA) was also isolated from the in vitro reaction mixture following incubation of NDPA with the microsomal fraction of rat liver. NHPPA could be oxidized further to form N-nitroso-2-oxopropylpropylamine (NOPPA). Administration of highly purified NOPPA to rats leads to formation of O(6)-methylguanine and 7-methylguanine in the ratio or 0.07. This ratio of the two methylated guanines is similar to that obtained following administration of N-nitrosodimethylamine (NDMA) at comparable dose levels, suggesting that the methylating agent formed from NOPPA is similar in reactivity to that formed from NDMA, and supporting the hypothesis that N-nitrosomethylpropylamine may be the methylating agent formed from NOPPA. (23 Refs)

4. INTERACTION OF REACTIVE INTERMEDIATES WITH DNA.

Magee PN, Chu CK, Gombar CT, Jensen DE, Parchman LG
Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Adv Exp Med Biol; 136(partB):1335-1347 1982

Covalent binding of some selected chemicals to rat liver DNA is described and the results related to the proposal by Lutz that the extent of binding may be a quantitative indicator in the process of chemical carcinogenesis. Lutz suggested that covalent binding may be expressed in quantitative terms as the Covalent Binding Index relating damage to DNA as a function of dose. N-nitrosodimethylamine was used as a positive control. No in vivo interaction of N-nitrosoproline with rat liver DNA was observed. Since this compound was rapidly eliminated from the body and a very small degree of metabolism occurred, the use of proline as a safe test compound in studies on endogenous nitrosation is supported in animals and humans. A very small, but real interaction between trichloroethylene and mouse liver DNA in vivo was observed, supporting the apparent low carcinogenic potency of the compound and doubts concerning its carcinogenicity. In the presence of sulfhydryl compounds, N-nitrosocimetidine interacted with calf thymus DNA in vitro, yielding a pattern of methylated purine bases identical to that produced by N-methyl-N'-nitro-N-nitrosoguanidine (MNG) and other carcinogenic and mutagenic N-nitroso compounds. Preliminary in vivo experiments indicated that the extent of methylation of DNA was much less in organs of animals treated with nitrosocimetidine than those treated with MNG. (37 Refs)

5. CONSTITUTIVE AND CARCINOGEN-DERIVED DNA BINDING AS A BASIS FOR THE ASSESSMENT OF POTENCY OF CHEMICAL CARCINOGENS.

Lutz WK
Inst. Toxicology, ETH, Univ. Zurich, CH-8603 Schwerzenbach, Switzerland
Adv Exp Med Biol; 136(partB):1349-1365 1982

The hypothesis that ground-level DNA damage is unavoidable and must be regarded as constitutive to a cell is presented. Sources for this type of damage include physiological reactive intermediates, nitrosamines, irradiation, carcinogenic metals, and viruses. Carcinogens are classified as initiating (DNA damaging, genotoxic) and nongenotoxic (act by modulating reactions and side reactions that increase or constitutive DNA damage or enhance the chance for such damage to proceed to a tumor). Carcinogenic potency of a carcinogen is defined as a product of persistent DNA damage x mutagenicity x nongenotoxic modulation of DNA damage. A correlation of DNA binding in vivo and the form of a 'Covalent Binding Index' (CBI) to the carcinogenic potency is shown. The CBI equals (micromole chemical bound/mole DNA nucleotides)/(millimole chemical administered/kg animal wt). Good linear correlation was found with an approx uncertainty of the estimate of a factor of 10 with a total span of values of 10(6). DNA binding is not enough to describe the potency of carcinogens; additional information is necessary to assess the organ specificity of initiating carcinogens. When administered alone, the nongenotoxic carcinogens appear to be much less potent than initiating carcinogens. Nongenotoxic carcinogens cannot be detected on the basis of chemical structure and short-term tests of their carcinogenic potency are not available. (21 Refs)

6. METABOLISM OF 2,4-DINITROTOLUENE BY RAT HEPATIC MICROSOMES AND CECAL FLORA.

Dent JG, Schnell SR, Guest D
Chemical Industry Inst. Toxicology, Res. Triangle Park, NC, 27709
Adv Exp Med Biol; 136(partA):431-436 1982

The metabolism of 2,4-dinitrotoluene (2,4-DNT) in hepatic microsomes and in the intestinal flora was investigated. Hepatic microsomes were obtained by preparation of livers from male Fischer 344 rats. Cecal microflora was obtained from male rats. [U-14C] 2,4-DNT was incubated at 100 uM with microsomes in 66 mM tris HCl (pH 7.4) for 1 hr; a NADPH generating system was included. An oxygen scavenging system was included in the incubations with nitrogen. The patterns of metabolites produced by the hepatic microsomes was dependent on the oxygen tensions in the incubations. In contrast to microsomes, cecal microflora did not metabolize 2,4-DNT in an air atmosphere, but the 2,4-DNT was rapidly reduced in anaerobic conditions. Both 2-and 4-nitroso-nitrotoluenes were detected in the cecal flora incubations. Comparison of the metabolism of the DNT by the cecal contents and the hepatic microsomes indicated that the reductive metabolic capacity of the cecal contents on a per g wet wt basis exceeds that of the liver by a factor of 1,000, suggesting that the cecum represents a major site for reductive metabolism of DNT; the 2,4-DNT undergoes reduction at either the 2 or 4 nitro group to a nitroso-nitrotoluene. Reduced metabolites of DNT absorbed from the gut would be substrates for the mixed function oxidase (MFO) enzymes in the liver. Oxidations by the MFO system would lead to highly reactive intermediates in the liver. Thus, the liver and cecal microflora acting in concert may be responsible for the carcinogenic activity of DNT. (7 Refs)

7. INVESTIGATIONS OF THE BIOACTIVATION OF N-NITROSOPYRROLIDINE IN THE RAT.

Cottrell RC, Lake BG, Phillips JC, Young PJ, Walters DG, Allars AJ, Gangolli SD
British Industrial Biological Res. Assoc., Carshalton, Surrey SM5 4DS, England
Adv Exp Med Biol; 136(partB):1165-1171 1982

Metabolism of N-nitrosopyrrolidine (NPYR) in rat liver is discussed. NPYR appears to competitively inhibit the conversion of N-nitrosodimethylamine (NDMA) to formaldehyde by rat liver 10,000 gravity supernatant preparations. A major difference between NYPR and NDMA was observed in the metabolism to 14CO2 by the isolated perfused liver. While the rate of conversion was sufficiently rapid to account for the rate observed in the intact animal, the rate of degradation of NYPR was consistently much slower in the isolated liver. At least three routes of biodegradation of NYPR occur in the rat. One route involves an initial rearrangement reaction, or apparent rearrangement to yield pyrrolidinone-2-oxime (PDO) which was detected radiolabeled in the urine of rats given a high dose of [2,5-14C]NYPR. A second route involves the generation of 4-hydroxybutanol which may be oxidized to 4-hydroxybutyric acid or its lactone. Both of these oxidation products were identified in rat urine. A third route yields 3-hydroxy-N-nitrosopyrrolidine (HNPYR) and, via further metabolism, C-1 pool precursors and CO2. Identification of radiolabel in urinary dimethylamine but not in methylamine, together with evidence from 3H/14C labeling experiments, indicates the generation of some C-1 pool precursors. PDO was synthesized and found to be relatively non-toxic to rats and inactive in the Ames system. The route via 4-hydroxybutanol has the potential to be an activating route. HNPYR is a mutagen in the Ames system without metabolic activation by rat liver S9; it appeared to be more active alone than NYPR with S9 activation. (13 Refs)

8. FORMATION OF 7-METHYLGUANINE IN LIVER DNA FROM RATS TREATED IN VIVO WITH N-NITROSOPYRROLIDINE (MEETING ABSTRACT)

Hunt EJ, Shank RC
Department of Commonunity and Environmental Medicine, Univeralty of California Southern Occupational Health Center, Irvine, CA, 92717
Toxicologist; 2(1):182 1982

It is known that 7-methylguanine (7-MG) is formed in liver DNA during hepatotoxicity induced by a variety of chemicals that cannot directly methylate DNA. In a study using radiolabeled N-nitrosopyrrolidine (NP), it was shown this hepatotoxin and hepatocarcinogen is not metabolized in the rat to an agent which methylates liver DNA guanine. 7-MG was detected in liver DNA of adult male Sprague-Dawley rats after administration of a hepatotoxic dose of NP using a highly sensitive high pressure liquid chromatography method which optically detects fluorescent alkylated purines in DNA hydrolysates without the need for radiolabel. Rats were given 14, 28, 57, 113, 225, 450, or 900 mg NP/kg body wt and decapitated 12 hr later; liver DNA was isolated, purified, and hydrolyzed at pH 7.0 or 1.0. The amount of 7-MG in liver DNA obtained at each dose level was 25, 64, 87, 58, 97, 112, 57 u mol per mol guanine, respectively. The detection of 7-MG in liver DNA of rats treated with NP is consistent with similar observations in liver DNA from rats treated with such diverse hepatotoxins as hydrazine, carbon tetrachloride, ethanol, phosphorus, bromobenzene, and puromycin. (2 Refs)

9. EVIDENCE FOR A PUTATIVE N-NITROSOPYRROLIDINE-DERIVED DNA ADDUCT (MEETING ABSTRACT)

Hunt EJ, Shank RC
Department of Community and Environmental Medicine, University of California Southern Occupational Health Center, Irvine, CA, 21955
Toxicologist; 2(1):68 1982

Many carcinogens, including dialkylnitrosamines, are thought to induce cancer through covalent binding of derivatives to target organ DNA. Some evidence suggests that N-nitrosopyrrolidine (NP) and other cyclic nitrosamines are at variance with this mechanism. Liver DNA was isolated 3, 6, 12, 18, 24, 30, or 36 hr after rats were given 900 mg NP/kg body wt po. The DNA was subjected to neutral thermal hydrolysis in pH 7 buffer for 1 hr at 100 degrees, and hydrolysates were fractionated by strong cation exchange high pressure liquid chromatography. Elution of fractions was monitored by fluorescence spectrophotometry. An unidentified fluorescent material was detected in all DNA hydrolysates from NP-treated rats, but not in hydrolysates from control animals. The putative adduct formed rapidly; the concentration of this material in liver DNA increased more than 3-fold from 3 to 12 hr following NP treatment, then began to gradually decrease over later times. The fluorescent material did not co-chromatograph with standard guanine derivatives methylated or ethylated in either the 7-or O6-position. The concentration of fluorescent material in liver DNA hydrolysates was dose-dependent in rats killed 12 hr after receiving 14, 28, 57, 113, 225, 450 or 900 mg NP/kg body wt. Neutral thermal hydrolysis is known to release 3-alkyladenine and 7-alkylguanine from DNA; alkylguanines fluoresce well, while alkyladenines do not. Hence, the putative DNA adduct in NP-treated rats may be a guanine derivative substituted in the 7-position. (1 Ref)

10. METABOLISM OF N'-NITROSONORNICOTINE BY CULTURED RAT ESOPHAGUS.

Hecht SS, Reiss B, Lin D, Williams GM
Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Carcinogenesis; 3(4):453-456 1982

The metabolism of N'-nitrosonornicotine (NNN), an esophageal carcinogen, by organ cultured F-344 rat esophagus was investigated. The major metabolites were separated by hplc and were identified by comparison to standards as 4-hydroxy-1-(3-pyridyl)-1-butanone, 4-hydroxy-4-(3-pyridyl)-1-butanol and 4-oxo-4-(3-pyridyl)butyric acid from 2'-hydroxylation of NNN and 4-hydroxy-4-(3-pyridyl)butyric acid from 5'-hydroxylation of NNN. These results demonstrate that alpha-hydroxylation, which leads to electrophilic diazohydroxides, is the major pathway of metabolism of NNN in cultured F-344 rat esophagus. The extents of formation of the metabolites increased with time and the ratio of products resulting from 2'-hydroxylation to those resulting from 5'-hydroxylation was 4.3 after 1 hr, 3.9 after 6 hr, 3.4 after 24 hr and 3.1 after 48 hr. F-344 rat liver slices from the same animals produced metabolites of NNN with a 2'/5'-hydroxylation ratio of 1.4. The 2'/5'-hydroxylation ratio in cultured Syrian golden hamster esophagus was 0.3. These results, together with those of parallel studies of NNN metabolism in A/J mouse lung and Syrian golden hamster trachea indicate that among these tissues, F-344 rat esophagus has a unique ability to preferentially hydroxylate the 2'-position of NNN. The results suggest that 2'-hydroxylation is the key step in the metabolic activation of NNN in rat esophagus. (Author abstract) (18 Refs)

11. METABOLISM OF CARCINOGENIC AND NON-CARCINOGENIC N-NITROSO-N-METHYLAMINOPYRIDINES. I. INVESTIGATIONS IN VITRO.

Heydt G, Eisenbrand G, Preussmann R
Inst. Toxicology and Chemotherapy, German Cancer Res. Center, D-6900 Heidelberg, W. Germany
Carcinogenesis; 3(4):445-448 1982

A comparative study of in vitro metabolism of isomeric N-nitroso-N-methylaminopyridines (NMPY) by rat liver microsomes revealed remarkable differences in the respective rates of potentially activating and deactivating processes. N-Nitroso-N-methyl-2-aminopyridine (2-NMPY), a potent carcinogen in rats and a mutagen in the Ames test was demethylated to a much greater extent than its non-carcinogenic and non-mutagenic isomers 3-NMPY and 4-NMPY. In contrast to the findings for 2-NMPY, enzymatic denitrosation and N-oxide formation play a substantial role in metabolism of 3-NMPY and 4-NMPY. The respective rates of presumed activating to deactivating metabolic processes were found to be approx 1.5 for 3-NMPY, 0.5 for 4-NMPY, but 3 for 2-NMPY at 10 mM substrate concentration. At 1 mM concentration (which is more close to the conditions prevailing in carcinogenicity experiments), however, the respective ratio for 2-NMPY was approx 50. 2-Hydroxypyridine, the hydrolysis product of the putative pyridine-2-diazonium intermediate, generated after oxidative demethylation, was formed in high yields from 2-NMPY. Only traces of 3-hydroxypyridine were formed from 3-NMPY and 4-hydroxypyridine could not be detected at all. Experimental evidence suggests that generation of 2-aminopyridine, which was found in high yields after incubation of 2-NMPY, is explained best by a secondary metabolic process: reductive cleavage of azo coupling products formed by reaction of the pyridine-2-diazonium intermediate with appropriate nucleophiles in the incubation mixture. (Author abstract) (8 Refs)

12. ANDROGEN REGULATION OF DMN-N-DEMETHYLASE ACTIVITY IN KIDNEY OF BALB/C MICE (MEETING ABSTRACT)

Mohla S, Ahir S, Ampy FR
Department of Oncology, Howard University College of Medicine, Washington, DC, 20060
Med Pediatr Oncol; 10(1):102 1982

Androgenic hormones have been shown to regulate the biotransformation of Dimethylnitrosamine (DMN) to its active mutagenic metabolite. This androgenic regulation in renal tissue is a receptor mediated phenomenon as androgens are not able to stimulate kidney microsomal enzymes required for Ames test, in Tfm mice. Further, even though hepatic enzymes are more active than the kidney enzymes, the androgen effect is tissue (kidney) specific. Recent observation indicates that this androgenic effect is observed only under conditions when androgen receptors are translocated in the nucleus. The present experiments were designed to test correlations between the mutagenic ability of renal tissue and its N-demethylase activity (an enzyme implicated in conversion of DMN to its active metabolite). N-demethylase activity was measured from micromosomal fractions of liver and kidney (by quantitating formaldehyde formation) according to Nash. The results indicate: (1) higher DMN-N-demethylase activity in liver (male or female, adults) compared to kidney (male or female); (2) higher enzyme activity in adult male compared to adult female renal tissue; (3) complete loss of renal but not liver enzyme activity in mice castrated for 7 days (testosterone treatment, 2 mg/day/10 days, can significantly increase enzyme activity of kidney tissues in such castrates); and (4) a significant increase in DMN-N-demethylase activity in renal tissue of testosterone treated adult female mice. These data indicate androgenic regulation in kidney DMN-N-demethylase activity. The BALB/c mouse kidney system is a useful model to study the mechanism(s) by which steroid hormones augment or inhibit biotransformation of procarcinogens to mutagens which may ultimately lead to tumorigenesis. (2 Refs)

13. THE EFFECT OF SUBSTRATES AND INHIBITORS OF MONOAMINE OXIDASE ON HEPATIC DIMETHYLNITROSAMINE METABOLISM AND MUTAGENICITY.

Lake BG, Rowland IR, Harris RA, Collins MA, Phillips JC, Cottrell RC, Gangolli SD
British Industrial Biological Res. Assoc., Woodmansterne Road, Carshalton, Surrey SM5 4DS, England
Adv Exp Med Biol; 136(partB):1143-1147 1982

Inhibition of both dimethylnitrosamine (DMN) metabolism and DMN-induced mutagenesis by substrates and inhibitors of monoamine oxidase (MAO) was studied using hepatic postmitochondrial supernatant fractions from male Sprague-Dawley rats. The addition of aminoacetonitrile and isoxazole markedly inhibited the metabolism of DMN to formaldehyde. However, both compounds had little effect on the activities of the two mixed function oxidase (MFO) enzymes ethylmorphine N-demethylase and aniline 4-hydroxylase. Similarly, benzimidazole and indazole inhibited the metabolism of DMN but not that of the two MFO substrates. DMN metabolism was also inhibited by the addition of the MAO substrates 2-phenylethylamine, tryptamine, and tyramine but not by cadaverine which is a substrate of diamine oxidase. Both MAO substrates and inhibitors were potent inhibitors of DMN-induced mutagenesis in the Ames test, whereas cadaverine had no effect. Neither MAO substrates nor MAO inhibitors had any marked effect on the mutagenesis of either aflatoxin B1 or benzo(a)pyrene. Both

these carcinogens are considered to be metabolically activated by enzymes of the MFO complex. Results demonstrated that a number of compounds of diverse chemical structures inhibit the metabolism and mutagenesis of DMN at concentrations which had little effect on several cytochrome P-450 dependent processes. As these compounds are either known substrates or inhibitors of MAO the results may suggest the participation of an enzyme with MAO-like properties in the hepatic metabolism/bioactivation of this nitrosoamine. (16 Refs)

14. THE EFFECT OF SUBSTRATES AND INHIBITORS OF MONOAMINE OXIDASE (MAO) ON HEPATIC DIMETHYLNITROSAMINE (DMN) METABOLISM AND MUTAGENICITY IN THE AMES TEST (MEETING ABSTRACT)

Lake BG, Rowland IR, Collins MA, Phillips JC, Cottrell RC, Gangolli SD
The British Industrial Biological Research Association, Carshalton, Surrey, SM5 4DS, England
Toxicologist; 2(1):172 1982

Dimethylnitrosamine (DMN), a potent hepatocarcinogen and mutagen, requires metabolic activation to exert its biological effects. Although it has been suggested that hepatic DMN metabolism is catalyzed by cytochrome P-450 dependent mixed function oxidase (MFO) enzymes, recent studies have provided evidence for several pathways of DMN metabolism. We have investigated the effect of a number of substrates and inhibitors of monoamine oxidase (MAO, EC 1.4.3.4) on DMN metabolism and DMN-induced mutagenicity. The metabolism of DMN for formaldehyde by rat hepatic postmitochondrial supernatant fractions was markedly inhibited by a number of MAO inhibitors (eg aminoacetonitrile, benzyl cyanide, indazole and pargyline) and by MAO substrates (eg benzylamine, 2-phenylethylamine, tryptamine and tyramine), but not by the deaminated aldehyde, acid and alcohol products of the latter class of compounds. At the concentrations which inhibited DMN metabolism the MAO substrates and inhibitors had little effect on a range of MFO enzyme activities. While the mutagenicity of DMN in the Ames test was markedly inhibited by MAO substrates and inhibitors, these compounds had little effect on the mutagenicity of either aflatoxin B1 or benzo(a)pyrene. (no Refs)

15. A NOVEL PATHWAY OF NITROSAMINE METABOLISM IN LIVER MICROSOMES: DENITROSATION OF NITROSAMINES BY CYTOCHROME P-450.

Schreak D, Schwarz M, Tennekes HA, Kunz W
German Cancer Res. Centre, Inst. Biochemistry, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Adv Exp Med Biol; 136(partB):1157-1164 1982

Denitrosation of nitrosamines by cytochrome P-450 (CP) and mechanistic aspects of nitrosamine denitrosation are discussed. The generation of nitrite in liver microsomes in vitro was shown to depend on N-nitrosomorpholine concentration and incubation time, and the reaction was markedly accelerated in liver microsomes from phenobarbital-pretreated animals. Nitrite formation was strongly inhibited by the addition of mono-oxygenase inhibitors, or by omission of NADPH. Pretreatment with 3-methylcholanthrene did not enhance denitrosation of nitrosamines in vitro. A strong correlation could be demonstrated between the rate of denitrosation of six different nitrosamines and their partition coefficients in CH2Cl2/H2O. The generation of nitrite from dimethylnitrosamine was strongly inhibited by the addition of superoxide scavengers, superoxide dismutase and epinephrine. Nitrite formation was affected only by the addition of a very high dose (80 milliMoles) of mannitol or benzoate. No significant changes in nitrite production could be detected in H2O2-supplemented liver microsomes. NO-CP complex formation has also been observed in samples of nitrosamines and dithionite-supplemented liver microsomes. Thus under anaerobic conditions, reductive cleavage of the N-N bond might also occur. Proposed pathways of nitrosamine denitrosation ultimately result in the generation of primary amines and primary and secondary hydroxylamines. (9 Refs)

16. DENITROSATION OF CARCINOSTATIC NITROSOUREAS BY PURIFIED NADPH CYTOCHROME P-450 REDUCTASE AND RAT LIVER MICROSOMES TO YIELD NITRIC OXIDE UNDER ANAEROBIC CONDITIONS.

Potter DW, Reed DJ
Dept. Biochemistry and Biophysics, Oregon State Univ., Corvallis, OR, 97331
Arch Biochem Biophys; 216(1):158-169 1982

Evidence establishing that the products of 2-chloroethyl nitrosourea denitrosation are nitric oxide (NO) and the parent urea is presented. NO formation during anaerobic microsomal denitrosation of 1,3-bis(-2-chloroethyl)-1-1-nitrosourea (BCNU) was demonstrated by determining NO binding to either ferrous cytochrome P-450 or hemoglobin which formed distinct Soret maxima at 444 and 415 nanometer, respectively. Further spectroscopic findings indicated that formation of the cytochrome P-450 ferrous-NO complex was catalyzed by NADPH-reduced microsomes. NO production during denitrosation of carmustine also was demonstrated by analysis of head gas of microsomal suspensions, which showed increasing NO concentrations with time. Determination of the cytochrome P-450 ferrous-NO optical extinction coefficient allowed the estimation of the denitrosation rates. Similar rates of 14C-labeled 1-(2-chloroethyl)-3-(cyclohexyl)-1-nitrosourea (CCNU) denitrosation to form labeled 1-(2-chloroethyl)-3-(cyclohexyl)-1-urea were observed. 14C-CCNU denitrosation by purified NADPH cytochrome P-450 reductase, noninhibited phenobarbital-induced microsomes and noninduced microsomes suggested a possible unique interaction of the NADPH cytochrome P-450 reductase and cytochrome P-450s in the cytochrome P-450 system. (40 Refs)

17. REACTION OF MICROSOMAL AND CYTOSOLIC ENZYMES WITH N-ARYLACETOHYDROXAMIC ACIDS IN THE PRESENCE OF OXYGEN.

Lenk W, Scharmer U
Pharmakologisches Institut, Universitat Munchen, Nussbaumstrasse 26, D-8000 Munchen 2, W. Germany
Adv Exp Med Biol; 136(partB):951-970 1982

Experiments on the metabolic fate of N-hydroxy-4-chloroacetanilide (N-OH-4ClAA), N-hydroxy-2-acetylaminofluorene (N-OH-2AAF), N-hydroxy-4-acetylaminobiphenyl (N-OH-4AAB), and N-hydroxyphenacetin (NHP) in rabbit or rat liver microsomal and cytosolic systems are reviewed. Differences in substrate affinity cause microsomal and cytosolic N-OH-2AAF, N-OH-4AAB, N-OH-4ClAA, and NHP to be N-deacylated at different rates, but the differences are not clear-cut enough to permit differentiation between carcinogenic polycyclic and noncarcinogenic monocyclic compounds. Differences in the rates of oxidation of the corresponding arylhydroxyamines were also detected, but these were likewise not clear enough for separation of respective poly- and monocyclic compounds.

Clear differences in reactivity between poly- and monocyclic nitrosoarenes were observed, but have not been related to toxicity of the corresponding N-arylacetohydroxamic acids. The prominent reactivity of N-OH-2AAF and of 2-nitrosofluorene suggests that the primary lesion, from which tumor growth is initiated, may be caused by this arylhydroxylamine and/or its N-arylacetohydroxamic acid. (38 Refs)

INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS

18. MORPHOLOGICAL AND CYTOCHEMICAL CHARACTERIZATION OF RAT HEPATOCYTES DURING CARCINOGENIC TRANSFORMATION INDUCED BY DIETHYLNITROSAMINE (DENA) (MEETING ABSTRACT)

Penasse W, Wanson JC, Bernaert D
No affiliation given
Acta Anat (Basel); 111(1/2):112 1981

Chemical hepatocarcinogenesis has been induced in adult Sprague-Dawley rats by administration of DENA at the final concentration of 70 mg/kg body weight, 24 h after partial hepatectomy. This process involves mainly three stages: preneoplastic foci already detectable 2 months after the treatment, hyperplastic nodules arising after about 9 months, and later on, hepatocarcinomas. A number of techniques were developed to study at the ultrastructural level the morphological modifications during the transformation process. Several enzymatic deficiencies affecting G6Pase and bile canalicular ATPase activities are associated with this process. These enzymatic activities constitute good markers for visualizing the evolution of the lesions and are finally the best tools for localizing these lesions by screening large surfaces of the liver making a bridge between the light microscope of the pathologist and the electron microscope of the ultrastructural knowledge. The study of this transformation with the transmission and the scanning electron microscope can be done on the cell in situ isolated by enzymatic perfusion from the liver, cultured in Petri dishes or in the whole extracted nodule. Preneoplastic hepatocytes display persistent phenotypic alterations: increase in size correlated with polyploidization, important storage of glycogen and lipids; cells frequently show an intense proliferation of the SER (smooth endoplasmic reticulum); the RER (rough endoplasmic reticulum) appears also disturbed and exhibits unusual structures. (no Refs)

19. AN EVALUATION OF DIMETHYLNITROSAMINE (DMN) - INDUCED HEPATOCELLULAR ALTERATIONS IN THE NEWBORN MOUSE MODEL USING HISTOCHEMICAL AND HISTOENZYMATIC MARKERS (MEETING ABSTRACT)

Cater KC, Gandolfi AJ, Sipes IG
Toxicology Program, University of Arizona, Tucson, AZ, 85724
Toxicologist; 2(1):99 1982

Newborn Swiss mice were dosed IP with 25 ug of DMN or saline, and at weaning placed on drinking water containing 0.05% phenobarbital (PB), a known promoter of hepatocellular carcinomas, or water alone. Preneoplastic foci (F) and hyperplastic nodules (HN) were identified histologically by two markers; resistance to exogenous iron accumulation and an increase in gamma-glutamyl transpeptidase (GGT) activity. F were distinguished from HN by size and by compression of the surrounding parenchymal cells. In the DMN and PB group, livers of affected male mice at 6,8,12 and 16 wk exhibited 6,10,17 and 12 iron resistant F/cm2 and 10,13,9 and 9 GGT-F/cm2, respectively. At these same time periods iron resistant-F in affected females ranged from 5-11 F/cm2, while GGT-F ranged from 9-16 F/cm2. Iron resistant HN were first observed in male mice at 8 wk; however, GGT-HN were not noted until 12 wk. By 12 and 16 wk affected males had 6 and 4 iron resistant HN/cm2 while affected females had 4 and 6, respectively. At these same time points, males had 6 and 3 GGT-HN/cm2 while females only displayed GGT-HN at 16 wk (6 HN/cm(2)). The DMN alone group contained an average of 4 F/cm2 (iron resistant or GGT) while no HN were noted in any group except the DMN and PB. Lung nodules were apparent as early as 6 wk in both sexes of the DMN alone group and at 12 wk in the DMN and PB group. (no Refs)

20. PRETREATMENT OF RATS WITH A SINGLE DOSE OF ACETYLAMINOFLUORENE INCREASES THE CAPACITY OF LIVER ENZYMES TO MOVE O6-METHYLGUANINE FROM DNA IN VIVO AND IN VITRO (MEETING ABSTRACT)

Cooper DP, Margison GP, O'Connor PJ
Christie Hospital, Manchester, England
Br J Cancer; 44(2):272 1981

Chronic pretreatment of rats with AAF (acetylaminofluorene) has been shown to enhance the repair of O6-methylguanine (O6-meG) and similar effects have now been obtained using single-dose pretreatments. Male Wistar rats were given AAF up to 20 mg/kg; ip 24 h before a single dose (1 mg/kg, ip) of [14C]-dimethylnitrosamine (DMN). Five h after the DMN challenge there were some variations in the amounts of 7-methylguanine (7-meG) and 3-methyladenine (3-meA) in the liver DNA of control and pretreated groups. However, the 3-meA/7-meG ratio was similar in all cases, while the O6-/7-meG ratio was reduced after 20 mg AAF/kg, suggesting that repair of O6-meG was enhanced. The effect was not specific for DMN-induced damage, as the repair of O6-meG produced in liver by MNU was also enhanced. Incubation of cell-free liver extracts with MNU-methylated DNA in vitro decreased the amount of O6-meG in the acid precipitable DNA. This decrease was protein-dependent, but no free O6-meG base was found in the acid supernatants. Extracts from control rats destroyed 21% of the O6-meG in the substrate, while extracts from animals pretreated with 6.67, 20 or 60 mg AAF/kg destroyed 40, 77 and 90% of the O6-meG respectively. The effects observed in vivo were therefore probably due to an increased production of repair enzyme. AAF pretreatment did not affect 7-meG glycosylase activity in cell-free extracts. There was a 20-fold increase in the incorporation of [3H]-dT into hepatic DNA of rats pretreated with 20 mg AAF/kg, while lower doses had no effect. The enhancement of O6-meG repair could therefore be related either to cell proliferation as a result of the hepatotoxicity of AAF or to the induction of repair enzymes in response to sublethal DNA damage. (1 Ref)

21. EFFECT OF AFLATOXIN B1 ON THE REPAIR OF O6-METHYLGUANINE IN THE HEPATIC DNA OF RATS AND MICE (MEETING ABSTRACT)

Maru GB, Margison GP, Chu YH, O'Connor PJ
Christie Hospital, Manchester, England
Br J Cancer; 44(2):273 1981

Pretreatment of male Wistar rats by ip injection of single (2 mg/kg) or multiple (4x0.5 mg/kg) doses of aflatoxin B1 (AFB)

stimulates the process for the removal of O6-methylguanine from hepatic DNA in animals challenged with a single dose (2 mg/kg) of [14C]-dimethylnitrosamine (DMN). The sensitivity of this system in terms of its ability to 'adapt', is indicated by the fact that the repair response can be detected as early as one day after pretreatment with a single dose. However, treatment of mice (C57Bl, males) with doses from 0.1 to 100 mg/kg of AFB, had no marked effect on the activity of the O6-meG repair system, when assayed in vitro using cell-free liver extracts and DNA methylated with [3H]-MNU as substrate. This murine repair system has been titrated in vivo, using a range of doses of [14C]-DMN (0.25-10 mg/kg). In terms of saturation kinetics it appears to be intermediate between the Syrian golden hamster and the rat but more closely resembling that for the rat. Different doses of AFB and exposure periods are under investigation, but it is tentatively concluded that the mouse, like the hamster and in contrast to the rat, is refractory to the inducibility of the O6-meG repair system. (3 Refs)

22. SOME EFFECTS OF CARCINOGENS ON CELL ORGANELLES.

Svoboda DJ, Reddy J
Dept. Pathology and Oncology, Univ. Kansas Coll. Health Sciences, Kansas City, KS
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Several observations regarding effects of carcinogens on cell ultrastructure published from 1972 through 1979 are reviewed. Carcinogens whose effect on cell organelles have been studied include the aflatoxins, diethylnitrosamine, dimethylnitrosamine, ethionine, pyrrolizidine, alkaloids, tannic acid, and thioacetamide. Changes caused by carcinogens include nuclear enlargement, increase in the number of nucleoli, conspicuous lysosomes, increase in the smooth endoplasmic reticulum (SER), detachment of ribosomes from the rough endoplasmic reticulum, zonal or diffuse decrease in glycogen, mitochondrial swelling, and a redistribution in the fibrillar and granular components of the nucleus. Most of the carcinogens, in the doses administered, caused slight to moderate necrosis and variable degrees of inflammatory infiltrate. In chronic studies, most of the carcinogens caused alterations either in the proportion or configuration of nucleolar components. There was an increase in interchromatin and perichromatin granules with ethionine and enlargement of interchromatinic spaces with thioacetamide. The most consistent cytoplasmic changes were increased SER and detachment of ribosomes from ergastoplasmic membranes. (210 Refs)

23. DNA ALKYLATION DURING CHRONIC DMN EXPOSURE OF MALE AND FEMALE C3H MICE (MEETING ABSTRACT)

Lindamood C, Billings KC, Bedell MA, Swenberg JA
Chemical Industry Institute of Toxicology, Research Triangle Park, NC
Toxicologist; 2(1):101 1982

The hepatocarcinogenicity of dimethylnitrosamine (DMN) is sex-dependent in C3H mice following chronic oral exposure. DMN causes predominently hepatomas in males and capillary endotheliomas in females. The purpose of this study was to assess the role of the promutagenic DNA lesion O6-methylguanine (O6MG), in the cellular specificity of DMN's carcinogenicity in C3H mice. Male and female mice were given 0 or 10 ppm DMN ad libitum in the drinking H2O for 2, 4 or 16 days. The DMN dosage varied from 1.74-2.14 mg/kg/day among the treatment groups. Livers were perfused in situ with collagenase and hepatocytes and nonparenchymal cells. (NPCs) separated by differential centrifugation. DNA was isolated by hydroxyapatite chromatography and purine bases separated by HPLC (high performance liquid chromatography) and quantitated from UV-absorbing and fluorescing peaks. Concentrations of 7-methylguanine (7-MG) in the 2 liver cell populations of both sexes increased between 2 and 4 days of exposure and remained relatively constant thereafter. NPCs of both sexes accumulated O6MG over the time course of DMN administration, such that increasing O6MG/MG ratios were observed. Male and female hepatocytes demonstrated increased removal of O6MG after exposure to DMN. Concentrations of hepatocellular O6MG in both sexes were 5 to 7 fold less at 16 days than at 4 days, resulting in decreased O6/7MG ratios. (1 Ref)

24. ACUTE EFFECTS OF DIEMTHYLNITROSAMINE (DMN) ON COMPOSITION AND SYNTHESIS OF RAT LIVER CHROMATIN PROTEINS (MEETING ABSTRACT)

Huang PH, Magee PN, Stewart BW
Temple University School of Medicine, Philadelphia, PA, 19140
Fed Proc; 41(3):687 1982

Administration to rats of the potent hepatocarcinogen DMN is followed by the methylation of hepatic nucleic acids and proteins. Consequent secondary structural changes in DNA may be detected by column chromatography on benzoylated DEAE (diethylaminoethyl)-cellulose. As part of the further investigation of nitrosamine-induced injury, short-term alterations in the composition of rat liver chromatin proteins have been analyzed. Administration of DMN (10 mg/kg) was associated with a proportional increase in the recovery of rat liver chromatin proteins for at least 48 hr after treatment and a biphasic increase in the incorporation of 14C-leucine into chromatin proteins. Upon further analysis of these proteins by one- and two-dimensional gel electrophoresis, changes in the histones and non-histone proteins electrophoretic mobility and staining intensity were detected. Incorporated 14C-leucine was distributed throughout all chromatin protein fractions analyzed 4 hr after DMN. During the period 24-48 hr, apparent preferential incorporation into histones occurred while at later times non-histone proteins were more highly radioactive. (no Refs)

25. CHANGES IN HEPATIC NONHISTONE CHROMOSOMAL PROTEINS (NHCP) DURING CARCINOGENESIS INDUCED BY DIVERSE CARCINOGENS (MEETING ABSTRACT)

Ramagli LS, Lee J, Becker FF, Rodriguez LV
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Fed Proc; 41(3):1176 1982

The NHCP of purified chromatins of normal, regenerating rat liver, stages in acetylaminofluorene (AAF) and diethylnitrosamine (DEN) carcinogenesis and resulting primary hepatocellular carcinomas (PHC) were analyzed by 2-dimensional polyacrylamide gel electrophoresis to detect changes in gene-controlling-proteins common to malignant evolution by diverse carcinogens. The NHCP were extracted with 3 M NaCl-7 M urea in Tris buffers containing phenylmethylsulfonylfluoride (PMSF), nucleic acids removed by ultracentrifugation, proteins recovered after dialysis by lyophilization and analyzed by 2-dimensional polyacrylamide electrophoresis and silver staining. A 7% qualitative difference in resolved NHCP was observed in AAF and DEN tissues but only 28% of these were in common. Approximately half of the changes detected in AAF and DEN treated tissues were found to reflect cell proliferative state, and, therefore, probably not correlated with malignant

conversion. Of the new proteins detected, none exhibited a molecular weight (MW) greater than 62,000 daltons (d). In addition to the appearance of new proteins, AAF and DEN, chromatins exhibited selective losses of proteins found in normal chromatins. These results indicate that while AAF and DEN produce a number of changes in NHCP unique to each carcinogen, only 6% are common and analysis of these might serve as logical starting points for continued studies. (no Refs)

26. PROTEIN COMPOSITION OF LIVER ENDOPLASMATIC RETICULUM IN NORMAL RATS AND IN RATS EXPOSED TO CARCINOGEN N-DIETHYLNITROSAMINE.

Berdinskikh NK, Mel'nikova NN, Livshits VI
R. E. Kavetskii Inst. Problem Oncology, Kiev, USSR
Vestn Akad Med Nauk SSSR; (3):48-52 1982

The changes of the protein composition of liver endoplasmatic reticulum (ER) were studied in random-bred albino rats exposed to N-diethylnitrosamine (DENA). Electrophoretic spectrum of ER proteins during DENA-induced hepatocarcinogenesis did not differ from that in normal liver. Analysis of protein composition of separated ribosomes showed decrease of the content of the fraction with mol wt of 50,000 daltons and increase of the content of fractions with mol wt of 150,000 and 170,000 daltons. The changes in the content of these three protein fractions were associated with the stages of DENA-induced hepatocarcinogenesis. (22 Refs) (In RUS)

27. LIPID COMPONENT OF MEMBRANES OF ENDOPLASMATIC RETICULUM OF RAT LIVER DURING CARCINOGENESIS INDUCED BY DIETHYLNITROSAMINE.

Berdinskikh NK, Sanina KL, Gula EP, Mel'nikova NN
R. E. Kavetskii Inst. Problem Oncology, Kiev, USSR
Vestn Akad Med Nauk SSSR; (3):53-57 1982

The effect of diethylnitrosamine (DENA) hepatocarcinogenesis on the phospholipid (PL) and cholesterol content in the liver endoplasmatic reticulum was studied in random-bred albino rats. The most pronounced increase of PL content was observed during the 1st and 20th wk of carcinogenesis. The increase of cholesterol content was detected only during the late stage of carcinogenesis. (14 Refs) (In RUS)

28. CHANGES IN ACTIVITIES OF URIDINE DIPHOSPHATE-GLUCURONYL-TRANSFERASES DURING CHEMICAL HEPATOCARCINOGENESIS.

Yin Z, Sato K, Tsuda H, Ito N
(c/o Sato) Second Dept. Biochemistry, Hirosaki Univ. Sch. Medicine, 5, Zaifu-cho, Hirosaki 036, Japan
Gan; 73(2):239-248 1982

Changes in the activities of hepatic uridine diphosphate-glucuronyltransferases (UDP-GTs) were investigated during the induction of hyperplastic nodules (enzyme-altered foci) by a system consisting of diethylnitrosamine (DEN) followed by N-2-fluorenylacetamide (FAA) and including partial hepatectomy. The activity of the late fetal form of UDP-GT, which was assayed towards o-aminophenol (o-GT activity), was induced rapidly by a single ip injection of DEN (200 mg/kg) or 3-methylcholanthrene (40 mg/kg) or by the continuous administration of FAA (0.02% in diet) alone. The activity further increased with the appearance of the nodules, while the activity of the neonatal form, which was assayed toward phenolphthalein (p-GT activity) and was inducible by phenobarbital, increased only slightly. The increased o-GT activity showed a good correlation with the increased number or area of enzyme-altered foci detected by gamma-glutamyltransferase activity staining, but the p-GT activity did not, though it was significantly increased. In hyperplastic nodules and well differentiated hepatomas induced by DEN (0.1% in drinking water, 3 wk) but isolated long after cessation of DEN, o-GT activity was markedly increased, but p-GT activity was decreased or remained at the level of normal rat liver. These data indicate that the increased o-GT activity may be one of the enzyme markers for preneoplastic hepatic cells. An antioxidant, butylated hydroxyanisole (BHA) (0.75% in diet), markedly elevated the hepatic o-GT activity rapidly after being administered with FAA in the above system, and the induction of the nodules was inhibited. (Author abstract) (32 Refs)

29. POLYAMINE METABOLISM IN MALIGNANT TUMORS.

Slatkin SP, Berezov TT
P. Lumumba Univ. People's Friendship, Moscow, USSR
Vestn Akad Med Nauk SSSR; (3):10-21 1982

The metabolism of polyamines (PA) was studied in random-bred albino rats with hepatoma 27 induced by diethylnitrosamine and in C3HA mice with hepatomas 22a, 61, 60, 48, and 46 induced by o-aminoazotoluene. PA content in hepatoma tissue was significantly greater than that in the normal liver. In all hepatomas except hepatoma 22a. The rate of ornithine carboxylation was significantly greater than that in the normal liver. All hepatomas were characterized by a virtual absence of diamine oxidase (DAO) activity. Significant increase of PA content and the increase of ornithine decarboxylase activity were observed 4-5 mo after the initiation of carcinogen administration, while the decrease of DAO activity was observed 1.5-3 mo after the initiation of the experiment. These findings indicate that the changes in the rate of PA oxidation can be considered as the primary manifestations of hepatocarcinogenesis, while the changes in ornithine decarboxylation reflect the tumor progression or dedifferentiation of tumor cells. (56 Refs) (In RUS)

30. IN VITRO INHIBITION OF DNA METHYLASE (DMASE) BY DIRECT CARCINOGENS AND THE PROTECTIVE ABILITY OF THIOL REDUCING AGENTS (MEETING ABSTRACT)

Chan JY, Ruchirawat M, Lapeyre JN, Becker FF
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Fed Proc; 41(3):685 1982

The role of DNA methylation during carcinogenesis is unknown although DNA from carcinogen-treated rat liver is hypomethylated. To determine if carcinogens directly affect DMase, the direct-acting carcinogens acetoxyacetylaminofluorene (AcAAF) and methylnitrosourea (MNU) were tested in vitro on DMase activity from rat liver. Fifty percent inhibition of DMase activity was achieved with 4.3 mM AcAAF and 47 mM MNU. The sensitivity of DMase towards direct carcinogens was similar to that for DNA polymerase-alpha, while DNA polymerase-beta, the putative repair enzyme, was highly resistant to carcinogen damage. When various thiol reducing agents were tested for their ability to protect DMase from carcinogen damage, differential protective ability was observed. Dithiothreitol, beta-mercaptoethanol and reduced glutathione were effective in protecting DMase from AcAAF damage while the effects of cysteine and ergothioneine were small. At 10 mM of these agents, the percent of

DMase activity recovered after interaction with 6.7 mM of AcAAF was 94,86,78,34 and 12, respectively. These effects may have some bearing on the DNA hypomethylation observed in vivo, suggesting that the carcinogens tested may achieve their inhibitory effect by affecting crucial thiol(s). These data also suggest that various intracellular thiols may play an important role in protecting DNA modifying enzymes from carcinogen damage. (no Refs)

31. EXPERIMENTAL STUDY OF THE BIOLOGICAL EFFECTS OF SMALL CONCENTRATIONS OF A MIXTURE OF DIMETHYLNITROSAMINE, DIMETHYLAMINE, AND NITROGEN DIOXIDE.

Prusakov VM, Benemanskii VV, Leshchenko ME, Katul'skii IuN
No affiliation given
Gig Sanit; (3):8-11 1982

The carcinogenic effect of combined exposure to a mixture of dimethylnitrosamine (DMNA), dimethylamine (DMA), and nitrogen dioxide (NDO) was studied in random-bred albino rats. The animals were subjected to a chronic, around-the-clock inhalation exposure to DMNA alone (0.07-0.66 mg/cubic meter) or in combination with DMA and NDO. The experiment continued for 1 yr. Analysis of the toxic effects DMNA alone and in combination with DMA and NDO showed wave-like changes in the RBC, WBC, and platelet counts. Exposure to DMNA resulted in a dose-dependent increase of liver and kidney tumors. Significant increase of the tumor yield after exposure to DMNA alone was observed for the doses of 19.2-44.2 mg/rat. DMNA in combination with DMA and NDO induced tumors at doses of 3.9-16.7 mg/rats. These findings are indicative of the synergism between DMNA, DMA, and NDO with respect to the carcinogenic activity and additive effect with respect to the general toxicity. (3 Refs) (In RUS)

32. ALTERATIONS OF BIOELECTRIC POTENTIAL IN PRIMARY HEPATOCELLULAR CARCINOMAS INDUCED BY N-2-FLUORENYLACETAMIDE OR DIETHYLNITROSAMINE.

Lai CN, Becker FF
(c/o Becker) Section Experimental Pathology, Dept. Pathology, Univ. Texas M. D. Anderson Hosp. and Tumor Inst. Houston, Houston, TX, 77030
Cancer Biochem Biophys; 6(1):1-6 1982

Primary hepatocellular carcinoma(s) induced in rats by N-2-fluorenylacetamide (AAF) or diethylnitrosamine (DEN) were examined for their bioelectric potential (EP). N-2-Fluorenylacetamide-induced PHC differed from age-matched normal livers by a mean of-12.9 mM, which is significant at p less than 0.001. They also differed from non-PHC-bearing surrounding liver by-4.75 mV, significant at p less than 0.05. Diethylnitrosamine-induced PHC differed from normal liver by-13.5 mV and from background liver by-9.95 mV, both significant at p less than 0.001. To determine the contribution of cell division to these differences, regenerating livers were examined. The levels of mixed function oxidases in PHC and in regenerating livers reported in the literature appeared to correlate with the measured EP. We, therefore, studied the effects of chemical inhibitors and an inducer of this enzyme system. The alterations of mixed function oxidase were demonstrated to parallel those of EP. (Author abstract) (35 Refs)

33. PARTICIPATION OF POLY(ADP-RIBOSYL)ATION IN THE DEPRESSION OF RNA SYNTHESIS CAUSED BY TREATMENT OF MOUSE LYMPHOMA CELLS WITH METHYLNITROSOUREA.

Taniguchi T, Agemori M, Kameshita I, Nishikimi M, Shizuta Y
Dept. Medical Chemistry, Kochi Medical Sch., Kochi 781-51, Japan
J Biol Chem; 257(8):4027-4030 1982

When mouse lymphoma cells (L-1210) are treated with methylnitrosourea, a DNA-damaging agent, polyadenosine diphosphoribose (poly(ADP-ribose)) synthetase activity increases five to eight-fold in 2-3 hr, while RNA polymerase activity remains constant for an initial 2 hr and then gradually decreases to 25-30% of the control level in 5 hr. Both alpha-amanitin-sensitive and -resistant RNA polymerase activities are depressed to the same degree by the treatment with methylnitrosourea. The depression in RNA synthesis is virtually prevented when the treated cells are cultured in the presence of 3-aminobenzamide, a specific inhibitor of poly(ADP-ribose) synthetase. Analyses of the RNA extracted from the cells labeled with [3H]uridine by agarose gel electrophoresis and by poly(U)-Sepharose column chromatography show that the contents of ribosomal precursor RNA and poly(A)-containing RNA are both low in the methylnitrosourea-treated cells as compared with those in the untreated cells and that the reduction in the contents of these kinds of RNA is almost completely prevented by the addition of 3-aminobenzamide to the culture medium. These results suggest that the enhancement of poly(ADP-ribosyl)ation causes the decrease in both synthesis of ribosomal RNA and messenger RNA. (Author abstract) (36 Refs)

34. ALKYLATION, PERSISTENCE OF DNA LESIONS, CELL SURVIVAL AND MUTATION IN 4 RODENT TUMOUR CELL LINES AFTER EXPOSURE TO N-METHYL-N-NITROSOUREA (MNU) (MEETING ABSTRACT)

Durrant L, Margison GP, Boyle JM
Christie Hospital, Manchester, England
Br J Cancer; 44(2):272 1981

Dose response curves for colony forming ability were determined following incubation with MNU for 30 min at 37C. The D0 values were 0.7, 0.3, 0.4 and 0.07 mM MNU for Chinese hamster cell lines V79 and V79/79, rat Yoshida sarcoma (YS), and mouse leukemia L1210 cells respectively. Induced mutation frequencies for resistance to 6-thioguanine were 13.8, 16.3 and 17.0x10(-4) per mM MNU for V79, V79/79 and L1210 respectively. The methylated purines O6-methylguanine (O6-meG), N7-methylguanine (N7-meG) and 3-methyladenine (3-meA) were determined on DNA hydrolysates extracted at various times after MNU exposure. There was good correlation between cell survival and total methylated purines for all cell lines except L1210, which showed excessive killing. The half-lives of N7-meG and 3-meA varied among the cell lines, from 15-30 h and 3.6-7.2 h respectively. The half-life of O6-meG was greater than 100 h, 21 hr, 5.7 h and 49.5 h in V79, V79/79, YS and L1210 respectively. Cell-free extracts of YS and L1210 were tested for their ability to destroy O6-meG when incubated with methylated DNA in vitro. The activity from YS was at least twice that from L1210. These results indicate that cell survival is not always related to the level of DNA alkylation, and induced mutation frequency does not correlate with the rate of O6-meG removal in these cell lines. (no Refs)

35. DNA DAMAGE, REPAIR AND DMBA METABOLISM IN HUMAN FETAL CELLS (MEETING ABSTRACT)

D'Ambrosio SM, Gibson-D'Ambrosio RE, Oravec C, Leong Y, Chang D
Departments of Pharmacology and Radiology, College of Medicine, The Ohio State University, Columbus, OH, 43210
Fed Proc; 41(3):1559 1982

The level of DNA damage, repair and replication following UV irradiation and N-ethyl-N-nitrosourea (ENU) treatment as well as the binding and metabolism of 7,12-dimethylbenz(a)anthracene (DMBA) was quantitated and compared in vitro in cells derived from human fetal brain, dermis, kidney, liver, intestine and lung. Using UDS (unscheduled DNA synthesis) as a measurement of DNA repair, fetal brain, kidney and liver cells exhibited lower (30-60%) levels of UDS than did fetal dermal, lung or intestinal cells treated with UV radiation or ENU. The order for repair of UV induced DNA damage was: dermal greater than lung greater than intestinal greater than kidney greater than liver greater than brain cells. The order for UDS following ENU treatment was: lung greater than dermal greater than intestinal greater than brain greater than liver cells. Intestinal cells metabolized DMBA approximately 30%, while brain cells metabolized only 2.6% of the DMBA. Liver, dermal, lung and kidney, metabolized 5-10% of the DMBA during a 48 hour period. Using HPLC (high pressure liquid chromatography), qualitative as well as quantitative differences in the metabolite profiles were observed in each cell culture. The level of DMBA binding to cellular DNA was of the order: intestinal greater than lung greater than liver greater than dermal greater than kidney cells. These studies provide, important information as to how various human fetal organs metabolize DMBA, repair DNA damage and replicate new DNA following carcinogen exposure. (no Refs)

36. KINETICS OF METHYL DAMAGES INDUCED BY N-14CH3-N-NITROSOUREA IN MICE BEARING EHRLICH ASCITES CARCINOMA.

Popov KN, Degterev IA, Zalkov GE
Inst. Chemical Physics, Moscow, USSR
Eksp Onkol; 4(2):54-58 1982

To evaluate the mechanism of the biological effects of methylnitrosourea (MNU), random-bred male mice bearing Ehrlich ascites carcinoma (EAC) were inoculated ip with 14C-MNU (50 mg/kg). Within different time periods after administration, animals were sacrificed and the distribution of labeled methyl group in EAC cells, liver, kidney, and spleen was determined. Characteristic feature of EAC cells was progressive accumulation of the labeled methyl group throughout the entire experiment. Increase of the label accumulation in the liver, kidneys, and spleen was detected only within the first hours after MNU administration. (14 Refs) (In RUS)

37. INDUCTION OF BLADDER CANCER IN RATS BY FRACTIONATED INTRAVESICULAR DOSES ON N-METHYL-N-NITROSOUREA.

Severs NJ, Barnes SH, Wright R, Hicks RM
(c/o Hicks) Dept. Cell Pathology, Sch. Pathology, Middlesex Hosp. Medical Sch., Riding House St., London W1P 7LD, England
Br J Cancer; 45(3):337-351 1982

Experiments were conducted to determine the dose response of rat bladder urothelium to a range of different single and fractionated intravesicular doses of the carcinogen, N-methyl-N-nitrosourea (MNU). A dose-related response of bladder-tumor incidence to single graded doses of MNU was found, and a threshold dose suitable for use in multistage carcinogenesis experiments was derived from these data. For any given total dose of MNU, the tumor incidence was greater if the MNU had been administered in several small fractions than if it had been administered in fewer larger ones. Extending the interval between doses did not reduce the tumor incidence. It is argued that these results support the multistage theory of carcinogenesis. The histopathology and cell-surface alterations which characterize the development of MNU-induced bladder cancer are described and the contribution of hyperplasia and calculi are discussed. (Author abstract) (39 Refs)

38. HIGH SUSCEPTIBILITY OF ANALBUMINAEMIC RATS TO INDUCED BLADDER CANCER.

Kakizoe T, Komatsu H, Honma Y, Nijima T, Kawachi T, Sugimura T, Nagase S
Natl. Cancer Centre Hosp., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan
Br J Cancer; 45(3):474-476 1982

Susceptibilities of 18 male Sprague Dawley (SD) rats and 16 analbuminemic (AAB) rats to N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN)-induced bladder cancer were examined. Rats were fed ad libitum on commercial CE-2 animal diet and given water containing 0.045-0.05% BBN for the first 8 wk of the experiment. The experiment was terminated after 20 wk due to the development of gross hematuria in AAB rats after 17 wk. Bladder cancer developed in all AAB rats (16/16 rats), but in only 3/18 of the SD group. Most of the tumors in the AAB rats were large almost completely filling the distended lumen of the bladder. The av wt of the bladder, including tumor in the AAB rats was 2.90 g and in SD rats was 0/19 g (15:1). The tumors were all transitional cell carcinomas associated with squamous metaplasia. Invasion of the muscular layer was observed in 3/16 AAB rats and in 1/18 SD rats. No bladder stones, hydronephrosis, distant metastases, or tumors in other organs were found. No tumors were found in untreated AAB (20 rats) and SD (18) animals. (7 Refs)

39. HISTOPATHOLOGICAL ANALYSIS OF PRENEOPLASTIC CHANGES DURING N-BUTYL-N-(4-HYDROXYBUTYL)-NITROSAMINE-INDUCED URINARY BLADDER CARCINOGENESIS IN RATS.

Fukushima S, Murasaki G, Hirose M, Nakanishi K, Hasegawa R, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Acta Pathol Jpn; 32(2):243-250 1982

Sequential microscopic alterations of the urinary bladder epithelium during carcinogenesis were examined in rats after oral administration of 0.01% or 0.05% N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN). Simple hyperplasia appeared after 4 wk of BBN administration. This regressed by 12 wk after BBN discontinuation but reappeared focally in some areas afer 20 wk and persisted to the termination of the experiment. Preneoplastic papillary or nodular hyperplasia appeared earlier and more frequently in rats treated with 0.05% BBN than in those treated with 0.01%, but these lesions regressed gradually during a prolonged observation period after BBN was discontinued. These results suggest that two types of papillary or nodular hyperplasias exist, one reversible and the other irreversible. Tumors appeared earlier in rats treated with 0.05% BBN than in those with 0.01% BBN. (Author abstract) (17 Refs)

40. HISTOCHEMISTRY OF NADH DIAPHORASE AND GAMMA-GLUTAMYLTRANSPEPTIDASE IN RAT BLADDER TUMORS.

Vanderlaan M, Fong S, King EB
Biomedical Sciences Div., Lawrence Livermore Natl. Lab., P.O. Box 5507, Livermore, CA, 94550
Carcinogenesis; 3(4):396-402 1982

To improve identification of preneoplastic bladder cancer cells, we have studied two enzyme histochemical changes in bladder tumors induced in male Fisher 344 rats by the carcinogen N-butyl-N-(4-hydroxybutyl)-nitrosamine. In early areas of focal nodular hyperplasia there was a dramatic increase in staining for NADH:menadione oxidoreductase (diaphorase) activity. In nonfocal areas as well, there were many individual cells with intense staining, while the controls were of uniform moderate staining. Large papillomas and carcinomas often showed heterogeneous staining. Gamma-glutamyltranspeptidase (GGT) was absent from normal urothelium and from all tumors except the most advanced carcinomas and large papillomas. In old, carcinogen-exposed animals, GGT activity was seen in the luminal surface of tumors and in the interlesion urothelium. In newborn rats and in rats with regenerative hyperplasia following wounding of the urothelium, the diaphorase staining was less than that in the untreated adult. Our findings suggest that increased diaphorase activity may serve to identify early islands of carcinogen-induced, enzymatically altered bladder cells, while GGT will not. (Author abstract) (23 Refs)

41. MEMBRANE MICROVISCOSITY INCREASES IN REGRESSING NITROSOMETHYLUREA (NMU) INDUCED MAMMARY CARCINOMA (MEETING ABSTRACT)

Dave JR, Knazek RA, Liu SC
Laboratory of Pathophysiology, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:938 1982

The objective of these studies was to determine if the changes observed in prolactin-binding capacity of membranes from growing and regressing NMU induced mammary carcinoma correlated with those observed in membrane microviscosity measurements. Buffalo female rats were intravenously injected with 5 mg/100 g body weight of NMU at 50, 80 and 110 days of age. Mammary tumors induced in Buffalo rats by treatment with NMU are known to regress after oophorectomy. These rats were, therefore, either sham operated or oophorectomized at 5 months of age and sacrificed at 1, 3, 4, 5 and 8 days after the surgery. The 100,000 x g membrane pellets of these growing or regressing tumors were used for PRL binding and fluidity studies. Membrane microviscosity was studied by fluorescence polarization at 24 C using a lipid probe 1,6 diphenylhexatriene (1 uM in PBS at pH 7.1). A 46% decrease in prolactin-binding capacity was observed in membranes obtained from animals sacrificed 8 days after oophorectomy. Such a decrease in prolactin binding capacity of membranes from regressing tumors is well documented. Fluorescence polarization values were low in membranes from growing tumors which increased progressively with time after oophorectomy, reaching a maximal value at 5 days after oophorectomy, the values being 0.140, 0.188, 0.226, 0.227, 0.248 and 0.250, for membranes from growing tumors and 1, 3, 4, 5 and 8 days regressing tumors, respectively. A similar difference in membrane fluorescence polarization values was observed in growing and regressing DMBA-induced mammary carcinoma. (no Refs)

42. RELATIONSHIP OF AGE AND STRAIN TO MAMMARY GLAND DNA DAMAGE, REPAIR AND REPLICATION IN VIVO (MEETING ABSTRACT)

Raber JM, Mhaskar DN, D'Ambrosio S
Departments of Pharmacology and Radiology, The Ohio State University, Columbus, OH, 43210
Fed Proc; 41(3):1559 1982

The incidence of mammary gland carcinogenesis depends strongly upon the age and strain of animal. In order to elucidate the underlying mechanisms responsible for these observations, we quantitated: a) the initial levels of alkali sensitive sites induced from a single dose of ENU (ethylnitrosourea) with the use of alkaline sucrose gradient sedimentation in rats both susceptible (Sprague Dawley [SD]) and resistant (Long Evans [LE]) to mammary gland carcinogenesis; b) the fate of such damage in female SD and LE rats at both 30 and 50 days of age; c) the degree of normal gland proliferation in both age groups; and d) the short term effect of ENU on normal mammary gland proliferation. An index of mammary gland proliferation was determined by incorporation of [3H]thymidine into mammary DNA over a two hour time period. Our data showed: a) the initial level of damage induced was higher in the 50 day than the 30 day old rat; b) the alkali labile sites appeared to decrease in both age groups, over the seven day period studied; c) loss of alkali labile sites appeared to be faster in the LE than in the SD rats; and d) normal mammary gland proliferation decreased after a single treatment with ENU. These data relate the induction and persistence of DNA damage (single strand breaks and alkali labile sites) in vivo to mammary gland carcinogenesis as a function of age and strain of rat. (no Refs)

43. DNA REPAIR AND REPLICATION IN MOUSE AND HUMAN LYMPHOCYTES FOLLOWING TREATMENT WITH DNA DAMAGING AGENTS (MEETING ABSTRACT)

Mhaskar DN, Reuter K, Whisler R, D'Ambrosio SM
Department of Pharmacology, The Ohio State University, Columbus, OH, 43210
Fed Proc; 41(3):1558 1982

The extent of DNA repair and replication was measured and compared in mouse spleen (MS) and human peripheral blood mononuclear cells (HPBMC) following in vivo (MS) and/or in vitro (MS and HPBMC) treatment with N-ethyl-N-nitrosourea (ENU), bleomycin (BLM) and/or ultraviolet radiation (UV). Both ENU and UV induced UDS in MC and HPBMC in culture. The ENU damage induced in MS in vivo appeared to be lost 24 hr post-treatment, since very low levels of UDS were observed compared to 1 hr post-injection. The level of UDS following a combination of ENU and UV were lower in HPBMC (50%) and MS (30%) treated in culture. ENU also inhibited 30% of the scheduled DNA synthesis (SDS) observed in HPBMC. BLM required the presence of the rat liver microsomes activation system for induction of UDS, but not for inhibition of SDS in MS and HPBMC in culture. BLM however did not appear to induce UDS in MS from mice treated in vivo, although it appeared to inhibit (50%) UDS following UV irradiation of MS cells. These data compares the differences and similarities between different types of DNA damaging agents given in vitro and in vivo and in mouse and human lymphocytes. (no Refs)

44. SELECTION OF METASTATIC VARIANTS FROM N-METHYL-N-NITROSOUREA-INDUCED RAT MAMMARY TUMOURS (MEETING ABSTRACT)

Williams JC, Gusterson BA, Coombes RC
Ludwig Institute for Cancer Research, London, England
Br J Cancer; 44(2):293 1981

N-methyl-N-nitrosourea (MNU) has been used to induce mammary adenocarcinomas in inbred strains of female rats; these tumors are hormone sensitive but do not spontaneously metastasize. Two methods have been used to derive spontaneously metastasizing tumors from MNU-induced primaries. A cell line has been isolated in vitro from a mammary adenocarcinoma induced in female F344/N rats. This strain of cells forms colonies in lungs of syngeneic animals when injected iv and forms tumors when injected im sc and into the mammary fat pad. Tumors growing in these 3 sites show a high incidence of metastasis to the lungs, and in the lymph nodes at lower incidence. A cell suspension obtained by enzymatic digestion of the same initial MNU-induced tumor formed lung colonies after iv injection. Colonies were tested for metastasis after reimplantation in the mammary fat pad. After 3 passages through the lungs a solid transplantable tumor has been obtained which metastasizes spontaneously to the lungs and lymph nodes. The tumors formed by the cell line and the transplantable tumors were histologically similar, showing glandular differentiation but including a spindle-cell component and areas of squamous differentiation. Metastases were morphologically similar. Both tumors and metastases contain measurable levels of cytoplasmic estrogen receptor. These systems may therefore constitute a useful model for the study of metastasis. (no Refs)

45. METASTATIC CAPACITY OF NITROSOMETHYLUREA-INDUCED RAT MAMMARY TUMOURS (MEETING ABSTRACT)

Williams J, Gusterson BA, Coombes RC
Royal Marsden Hospital, Sutton, Surrey, England
VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

Nitrosomethylurea (NMU) has been used to induce mammary adenocarcinomas in inbred female rats: these tumors are hormone-sensitive but do not spontaneously metastasize. Three methods have been used to derive metastasizing tumors from NMU-induced primaries. 1) Primary tumors have been transplanted into the mammary fat pad of syngeneic animals. 2) A cell strain has been isolated in vitro which formed tumors in syngeneic animals when injected into a number of sites. Tumors growing subcutaneously showed a high incidence of metastasis formation in the lungs and in the lymph nodes at lower incidence. 3) A cell suspension obtained by enzymatic digestion of a NMU-induced tumor formed lung colonies after iv injection. Colonies were tested for spontaenous metastasis by reimplantation in the mammary fat pad. After 3 passages through the lungs a solid transplantable tumor was obtained which showed metastasis to lungs and lymph nodes. The tumors formed by the cell line and the transplantable tumor were histologically similar showing glandular differentiation but including a spindle cell component and areas of squamous differentiation. Metastases were morphologically similar. These systems may constitute a useful model of human breast cancer. (1 Ref)

46. MECHANISM OF ORGAN-SPECIFIC TUMOR INDUCTION IN THE GASTRO-INTESTINAL TRACT (MEETING ABSTRACT)

Kleihues P
Universitat Freiburg, Albertstrasse 19, D 7800 Freiburg, W. Germany
J Cancer Res Clin Oncol; 103(Suppl):A11 1982

The metabolism and reaction with DNA of three carcinogens was investigated after systemic administration selectively induced tumors in different segments of the gastro-intestinal tract. These agents share a common ultimate carcinogen, methyl diazonium ion, and produce an identical pattern of methylated DNA bases. Following oral or systemic administration in rats, N-nitrosomethylbenzylamine (MBN) induced a high incidence of esophageal carcinomas. Methylation of DNA purines by a single iv dose of (methyl-14C) MBN is most extensive in the esophagus, followed by liver, lung and forestromach. In mice, systemic application of MBN resulted in the development of forestomach carcinomas as in this species, DNA methylation by MBN is higher in forestomach than in esophageal DNA. The alternative possibility of enzymic hydroxylation of the methyl group of MBN cannot be ruled out but after administration of (methylene-14C) MBN no benzylated DNA bases were detected in rat tissues. Methyl(acetoxymethyl)nitrosamine (DMN-OAc) is a stable derivative of the alpha-hydroxy intermediate of dimethylnitrosamine. Heterolytic decomposition of DMN-OAc occurs through esterase mediated cleavage of the acetoxy moiety. Following iv injection of (14C)DMN-OAc by far the highest levels of DNA alkylation were found in the lung, the principal target organ for this route of application. In contrast, ip injection of (14C) CMN-OAc resulted with a preferential alkylation of organs bordering the abdominal cavity with highest values in ileum and colon, the target organs for this route of application. Weekly sc injection of 1,2-dimethylhydrazine (DMH) in rats and mice cause a selective induction of colon carcinomas. Alkylation of DNA purines by DMH was highest in liver, followed by colon, kidney and ileum. (no Refs)

47. HISTOPATHOLOGY OF EARLY STAGES IN EXPERIMENTAL GASTRIC CARCINOMA (MEETING ABSTRACT)

Schlake W
Pathologisches Institut der Westfallischen Wilhelms-Universitat, Domagkstrasse 17, D 4400 Munster, W. Germany
J Cancer Res Clin Oncol; 103(Suppl):A12 1982

Since the reports of Sugimura et al (1967) on the carcinogenicity of N-methyl-N-'-nitro-N-nitrosoguanidine (MNNG), numerous authors have published a wealth of histopathologic data on chemically induced gastric carcinoma. However, interpretation and classification of histologic findings in pre-cancerous and pre-invasive stages of experimental gastric cancer are still far from coherent. Combined with a review of findings documented in the literature, the analysis of our own extensive studies resulted in a concept of three possible modes of carcinoma development: 1) lumen-oriented hyperplasia (exophytic adenomatous growth) leading to polypous adenocarcinoma; 2) serosa-oriented adenomatous proliferation (hyperplasia) with increasing cellular atypia leading to infiltration and transformation into carcinoma; 3) direct invasion of atypical 'tumor cells' into the mucosal stroma unpreceded by mucosal hyperplasia. The specific features of carcinogenesis in the operated stomach reflect the change in anatomical conditions provoked by the surgical traumatization of the mucosa, and the resulting change of proliferation kinetics. Experimental data on the stages of

carcinogenesis may be compared with analogous findings in the human stomach after gastric surgery. (no Refs)

48. PANCREATIC CARCINOMA INDUCED BY N-METHYL-N'-NITROSOUREA IN AGED MICE.

Zimmerman JA, Trombetta LD, Carter TH, Weisbroth SH
Dept. Biological Sciences, St. John's Univ., Jamaica, NY, 11439
Gerontology; 28(2):114-120 1982

We have studied the ability of N-methyl-N'-nitrosourea to induce pancreatic carcinoma within 5 mo when single doses were administered to C57BL/6J male mice at 3, 12 and 24 mo of age. Pancreatic tumors were not observed in the young and middle-aged animals, but 3/15 of the surviving aged mice showed gross evidence of carcinoma. Ultrastructural analysis revealed in each tumor the presence of two populations of undifferentiated cells, both cell types possibly being of acinar cell origin. The observation of pancreatic carcinoma only in aged animals treated with an environmental carcinogen may be a model paralleling the human condition, which also shows a strong age dependency. (Author abstract) (25 Refs)

49. ENDOSCOPIC DIAGNOSIS OF CHEMICALLY INDUCED AUTOCHTHONOUS COLONIC TUMORS IN RATS.

Merz R, Wagner I, Habs M, Schmahl D, Amberger H, Bachmann U (c/o Habs) Institut fur Toxikologie und Chemotherapie, DKFZ, Postfach 101949, 6900 Heidelberg 1, W. Germany
Hepatogastroenterology; 28(1):53-57 1981

The suitability of using coloscopy as a diagnostic method is investigated with respect to colonic carcinomas induced locally by the administration of N-nitrosoacetoxymethylmethylamine, N-methyl-N-nitrosourea, and methylnitronitrosoguanidine, or systemically by sc injection of 1,2-dimethylhydrazine in Sprague-Dawley rats. The endoscopic diagnostic examination proved to be clearly superior to methods of animal inspection, palpation, investigation for occult blood, and exploratory laparotomy which have so far been employed in animal experiments with small rodents. The relevance of this method is discussed for the early detection of chemically induced colonic tumors, and the observation of tumor development under experimental cytostatic therapy. (Author abstract) (34 Refs)

50. EXPERIMENTAL TUMORS OF THE PERIPHERAL NERVOUS SYSTEM.

Beniashvili DS
Cancer Res. Center, Tbilisi, USSR
Eksp Onkol; 4(2):12-19 1982

Incidence of spontaneous and induced tumors of the peripheral nervous system (PNS) in the experimental animals is reviewed. PNS neoplasms were induced after sc or im applications of polycyclic hydrocarbons. Injection of methylcholanthrene into the sciatic nerve produced tumors in rabbits and in random-bred rats. The spectrum of nitrosamine-induced PNS tumors was shown to depend upon the animal species, age, strain, dose, and the mode of administration. Prolonged iv administration of methylnitrosourea (MNU) resulted in selective induction of CNS and PNS tumors. High incidence of neurogenic tumors was recorded in Fisher and BD-IX rats. Ethylnitrosourea (ENU) showed high affinity to PNS during transplacental carcinogenesis. Sensitivity of rat embryo to ENU was 30-50x greater than that of the adult rats. The highest incidence of PNS tumors was observed after ENU administration during the last third of the gestation. Nitroso compounds and urethane were reported to induce tumors of the sympathetic nervous system in rabbits, hamsters, and rats. (103 Refs) (In RUS)

51. DERIVATION AND PROPERTIES OF CELL LINE OF RAT BRAIN GLIOMA.

Zhmareva EN
Res. Inst. Neurosurgery, Kiev, USSR
Eksp Onkol; 4(2):27-30 1982

A method of culturing brain glioma cells (glioma 2211) is described. The original tumor was induced in a random-bred rat subjected to repeated administration of methylnitrosourea (10 mg/kg). Culturing of glioma 2211 cells resulted in progressive increase of the volume of cytoplasm, flattening of cells, and formation of a more compact monolayer. Glioma 2211 cells contained the glia-specific protein S-100. (14 Refs) (In RUS)

52. STRAIN DIFFERENCES OF TUMORIGENIC EFFECT OF NEONATALLY ADMINISTERED N-ETHYL-N-NITROSOUREA IN RATS.

Naito M, Naito Y, Ito A
Dept. Cancer Res., Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi 1-2-3, Minami-ku, Hiroshima 734, Japan
Gan; 73(2):323-331 1982

The tumorigenicity of neonatally administered N-ethyl-N-nitrosourea (ENU) was studied in four different inbred strain rats, that is Wistar/Furth (WF), Long-Evans (LE), F1 of Wistar/Furth and Long-Evans (F1) and Fischer 344 (F344) rats. All strains developed tumors of the nervous system with high incidence (97 to approx 100%) during 6 mo of observation. The incidence of tumor of the central nervous system, including the brain (82 to approx 88%) and the spinal cord (53 to approx 76%), was high in all strains, but that of the peripheral nervous system, including the cranial nerve (21 to approx 89%) and the spinal root (13 to approx 93%), differed by strain. The peripheral nervous system of WF and F344 rats had a low susceptibility to the tumorigenic effect of ENU, but that of LE rats had a high susceptibility. Many brain tumors were induced in the temporal and frontal cortex and subcortex in all strains of rats. Spinal cord tumors were observed at all levels of the white matter of the spinal cord without any predilection site. Spinal root tumors were located in lumbosacral plexuses in WF and F344 rats, but in Le and F1 rats cervical and thoracic root tumors were also observed. Histological examination revealed that most of the brain and spinal cord tumors were oligodendroglioma, but in F344 rats about half of the brain tumors were mixed glioma. Epidermoid cysts of the lumbar spinal cord were observed only in F344 rats. Tumors of the peripheral nervous system were so-called anaplastic schwannoma. (Author abstract) (23 Refs)

53. THE EFFECTS OF METHYLNITROSOUREA ON RETINAL MORPHOLOGY: A DESCRIPTIVE ANALYSIS (MEETING ABSTRACT)

Yielding KL, Jirakulsomchok S, Chronister RB
Department of Anatomy, University of South Alabama, Mobile, AL
Anat Rec; 202(3):212A 1982

The present report describes some characteristics of retinal lesions, similar to some aspects of retinoblastomas, which are produced by transplacental injections of methylnitrosourea (MNU), a DNA alkylating agent. MNU was injected into pregnant SAF/ICR, Swiss, CD-1 and A/J mice on days 16-17 of gestation. Animals were killed 3 weeks-6 months postnatally and the eyes embedded in either paraffin or methacrylate. Pups

exposed to saline alone were controls. The retinal damage was striking. Low doses of MNU (5 mg/kg) produced dysplasia primarily at the periphery near the ora serrata. Large doses (50 mg/kg) produced severe retinal atrophy and cataracts. Moderate doses (10-20 mg/kg) produced retinal atrophy consistently. The dysplasia was characterized by both atrophy and the formation of either rosettes or alterations in the formation of receptor elements. The atrophy was characterized by a marked diminution (most pronounced in CD-1 and Swiss mice) in the number of cells present in the retina. Alterations in either receptor formation or outer nuclear layer configuration were dose dependent. In lower doses, simple deviations were noted in the orientation of the outer nuclear layer. Larger doses (15-20 mg/kg) produced consistent rosette formation. Serial section reconstruction of the rosettes revealed that they were tube-like structures completely surrounded by cells (generally outer nuclear layer cells). Furthermore, the cells rested upon the outer limiting membrane. In many cases, the receptor processes of these outer nuclear layer cells extended into the central part of the rosette. (no Refs)

54. ESTABLISHMENT AND CHARACTERISTICS OF THE HEPATOMA CELL LINES FSK 7901 AND FSK 7902 OF THE RAT.

Gong M
Dept. Histology and Embryology, Fouth Army Medical Coll., People's Republic of China
Acta Anat Sin; 12(3):299-303 1981

The establishment and characteristics of two hepatoma cell lines from male rats are described. The hepatomas were induced in rats by feeding diethylnitrosamine and the tumor cell lines were obtained by cell culture of the tumor nodules. FSK 7901 had been maintained for 557 days and FSK 7902 for 524 days. The chromosome number of most cells of the two cell lines ranged between 63 and 84. The major characteristics of FSK 7901 included the following: (1) cells were densely arranged, (2) small hepatoma cells were distributed regularly within or around the new growth area, (3) acidophilic region next to nucleus was large and distinct, nucleoli were large and few in number, and (5) cell growth was slow. Compared to FSK 7901, cells of FSK 7902 were loosely arranged, its small hepatoma cells were irregularly distributed, its acidophilic area next to the nucleus was smaller and less distinct, cell nucleoli were small in size and abundant, and cell growth was faster. (14 Refs) (In CHI)

MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS

55. INHIBITION OF THE HEPATOCARCINOGENIC ACTIVITY OF DIETHYLNITROSAMINE (DENA) BY ETHANOL IN RATS.

Habs M, Schmahl D
Institut fur Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
Hepatogastroenterology; 28(5):242-244 1981

Male Sprague-Dawley rats received 0.1 mg/kg of diethylnitrosamine orally 5 times a wk for life with or without additional subsequent administration of 5 ml/rat/day of a 25% aqueous solution of ethanol. The additional treatment with ethanol significantly reduced the induction of liver cancer, but not of esophageal tumors. These findings do not support speculations based on epidemiologic studies as to a cancer-causing effect of alcohol. (Author abstract) (11 Refs)

56. EFFECTS OF ALPHA-NAPHTHYLISOTHIOCYANATE, LITHOCHOLIC ACID AND SELECTED HEPATOCARCINOGENS ON EPOXIDE HYDROLASE, DT-DIAPHORASE AND SERUM INDICATORS OF CHOLESTASIS (MEETING ABSTRACT)

Thompson MB, Dent JG, Graichen ME, Neptun DA, Scortichini BH, Popp JA
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
Toxicologist; 2(1):101 1982

The classic cholestatic agent alpha-naphthylisothiocyanate (ANIT) elevates the hepatic preneoplastic marker epoxide hydrolase (EH). Abilities of 3 hepatocarcinogens and 2 cholestatic agents to produce cholestasis and enhance hepatic EH activity were compared. Hepatocarcinogens 2-acetylaminofluorene (AAF) at 100 ppm or 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB) at 600 ppm in the diets or diethylnitrosamine (DEN) at 40 ppm in the drinking water were given to male, Fischer-344 rats (200-270 g). The cholestatic agents ANIT at 1000 ppm or lithocholic acid (LA) at 10,000 ppm in the diets were fed to comparable groups. Concentrations of total bile acids (BA), total cholesterol (CH) and total bilirubin (BIL) and the activity of gamma-glutamyltranspeptidase (GGT) were measured in serum at 2, 4 and 6 weeks. Activities of hepatic microsomal epoxide hydrolase (EH) and cytosolic DT-diaphorase (DTD) were determined. Serum BA concentrations were increased by all treatments. ANIT treatments produced the greatest increases. AAF and 3'-MeDAB caused intermediate increases and DEN and LA the smallest. CH and BIL concentrations and activities of GGT and DTD were only increased by treatment with ANIT. EH was increased by all treatments except LA. At 2 and 6 weeks animals exposed to AAF, DEN and 3'-MeDAB had a direct correlation between serum BA and EH activities. (no Refs)

57. COCARCINOGENICITY OF SACCHARIN TOWARD N-DIBUTYL-NITROSAMINE CARCINOGENICITY IN RAT LIVER AND URINARY BLADDER (MEETING ABSTRACT)

Pereira MA, Britt AL
Health Effects Research Laboratory, US Environmental Protection Agency, Cincinnati, OH
Toxicologist; 2(1):64 1982

Saccharin has been demonstrated to be a promoter of chemical carcinogenesis in the rat urinary bladder. Since other tumor promoters are also cocarcinogens, we evaluated the possibility that saccharin is also a cocarcinogen. Male Fisher 344 rats simultaneously received 0.02% dibutylnitrosamine (DBN) in their drinking water and 5% sodium saccharin in their diet for a total of 26 weeks. The liver of rats that received only DBN contained 16 hyperplastic nodules among 5 of 29 (17%) animals and 2 hepatocellular carcinomas in 1 of 29 (3%) of the animals. The simultaneous administration of sodium saccharin to the animals that received DBN, produced an enhanced hepatocarcinogenic response of 106 hyperplastic nodules in 17 of 21 (81%) animals and 81 hepatocellular carcinomas in 17 of 21 (81%) animals. The number of preneoplastic focal alterations in the liver that were induced by DBN, was also enhanced by sodium saccharin. The livers of untreated control rats and rats that received only sodium saccharin were free of preneoplastic

foci, hyperplastic nodules and hepatocellular carcinomas. In the urinary bladder, treatment with DBN produced simple and nodule hyperplasia that was enhanced by simultaneous treatment with saccharin. Sodium saccharin did not result in either a preneoplastic hyperplasia or a neoplastic response in the urinary bladder of the rats. (no Refs)

58. DIFFERENTIAL EFFECTS OF DIETARY ANTIOXIDANTS OF CHEMICAL CARCINOGENESIS (MEETING ABSTRACT)

King MM, McCay PB
Oklahoma Medical Research Foundation, Oklahoma City, OK, 73104
Fed Proc; 41(3):358 1982

Female weanling Sprague-Dawley rats were fed a defined semipurified diet with antioxidants being supplemented throughout the experiments as indicated. In one set of experiments, the diets were supplemented with butylated hydroxytoluene (BHT). The rats were given a 10 mg oral dose of 7,12-dimethylbenz(a)anthracene at 50 days of age. The incidence of mammary adenocarcinomas was markedly lower in the BHT-supplemented rats compared to rats fed the same diet without BHT. When butylated hydroxyanisole (BHA) was supplemented in the diet instead of BHT, no inhibition of mammary tumor development was observed. In similar experiments, it was found that propyl gallate supplementation also offers protection against DMBA-induced tumorigenesis while alpha-tocopherol does not. These results raise the question: is the antioxidant property of the supplement actually related to inhibition of tumorigenesis or is it some other property of particular antioxidants (in this case, BHT and propyl gallate)? To determine if BHT may possibly be affecting some metabolic system associated with the activation of DMBA to the ultimate carcinogen, the effect of BHT supplementation on tumor induction was compared between a direct acting mammary carcinogen (nitrosomethylurea) and DMBA, which does require metabolic activation. BHT inhibited DMBA- but not NMU-induced mammary tumorigenesis, suggesting that the influence of BHT may involve inhibition of DMBA activation. (no Refs)

59. NICOTINE INFLUENCE UPON THE DEVELOPMENT OF EXPERIMENTAL STOMACH TUMORS.

Gurkalo VK, Volfson NI
Lab. Carcinogenic Agents, Petrov Res. Inst. Oncology, 68 Leningradskaya St., Pesochny-2, Leningrad 188646, USSR
Arch Geschwulstforsch; 52(4):259-265 1982

The ability of nicotine (NC) to modify the carcinogenic effect of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) was studied in rats. Eighty-five male random bred white rats were divided into two series. The total MNNG dose was av 162.7 mg/animal in the Group 1 of the first series and 166.2 mg/animal in Group 2 of the first series. Group 2 animals also received 0.5 mg/kg NC sc 3x/wk. Group 3 animals (genetic controls) received neither MNNG nor NC. The 25 rats in the second series were studied for acetylcholinesterase activity in cerebrum, hypothalamus, and medulla. Rat stomach wall slices were studied microscopically. After several wk, the specific sequential structural modifications of glands developed, accompanied by persistent non-specific changes, in MNNG-exposed rats. Different signs of non-specific changes were observed in stomachs of all Group 1 and Group 2 rats. The simplification of glandular structure was marked. A number of rats in Groups 1 and 2 showed signs of buds and shoots developing in the middle and basal parts of the wall glands. These changes were accompanied by the formation of short branching and cystically epithelial complexes with signs of atypia. Fifty percent of Group 1 and 67% of Group 2 rats showed more advanced changes of epithelial complexes sprouting into the stomach wall. Malignization and formation of adenocarcinomas were observed in all such cases. The multicentric character of the induced specific pathological changes was especially well expressed in Group 2 animals. No spontaneous precancerous changes or cancer of the stomach were found in Group 3 rats. Results showed that animals subjected to the combined MNNG and NC treatment developed stomach cancers earlier and at double the frequency of control animals. NC enhanced the carcinogenic effect of MNNG. (30 Refs)

60. ASSESSMENT OF THE CAPACITY OF 3,3',4,4',5,5'-HEXABROMOBIPHENYL TO SERVE AS A PROMOTER OF HEPATOCARCINOGENESIS (MEETING ABSTRACT)

Jensen RK, Sleight SD, Goodman JI, Millis CD, Aust SD, Trosko JE
Department of Pathology, Michigan State University, East Lansing, MI, 48824
Toxicologist; 2(1):99 1982

The objective of this study was to determine if 3,3',4,4',5,5'-hexabromobiphenyl (HBB) can act as a promoter of hepatocarcinogenesis. This congener and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) are similar in that they both cause 3-methylcholanthrene type induction of hepatic microsomal drug-metabolizing enzymes and produce a similar and characteristic pattern of toxic and histologic responses. TCDD has been shown to be a promoter of hepatic cancer in rats. To test the tumor promoting capacity of HBB, female Sprague-Dawley rats weighing 200-250 g were injected ip with diethylnitrosamine (DEN) at a dose of 10 mg/kg 24 hours after a 2/3 partial hepatectomy (PH). Thirty days after PH, groups of 6 rats were fed control diets or diets containing 1 ppm HBB or 500 ppm phenobarbital (Pb). Groups of 3 rats without prior hepatectomy or DEN were fed the same diets. At 6 months, rats were killed and samples were collected for histologic and histochemical evaluation. Gamma glutamyl transpeptidase (GGT) was used to identify enzyme altered foci. The average number of GGT positive foci/cm2 were: control, 0; Pb, 58; HBB, 79. Values for rats not hepatectomized or given DEN were: control, 0; HBB, 11. Rats fed HBB had decreased weight gain and thymic atrophy. Histologically, the liver had severe hepatocellular swelling and vacuolation and focal areas of necrosis. (no Refs)

61. DINITROTOLUENE PROMOTION OF DIETHYLNITROSAMINE (DEN) INITIATED HEPATOCYTES IN VIVO (MEETING ABSTRACT)

Leonard TB, Popp JA
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
Toxicologist; 2(1):100 1982

Technical grade DNT (dinitrotoluene) (tDNT) is a potent hepatocarcinogen when fed to F-344 male rats for one year (100% incidence of hepatocellular carcinomas). The present studies were designed to ascertain whether tDNT had promoting activity and to investigate the mechanism of tDNT promotion. Male F-344 rats were treated with a single dose of DEN (150 mg/kg), permitted to recover for 2 wk, and then fed tDNT in the diet for 3 wk. Promotion activity was quantitated by determining the incidence of histochemically identifiable hepatic gamma-glutamyl transpeptidase positive (GGT+) foci. Feeding 14 mg/kg/day and 35 mg/kg/day of tDNT caused a dose-dependent increase in GGT+ foci relative to initiation control and promotion control values. To investigate the

mechanism of tDNT promotion, the effectiveness of tDNT (35 mg/kg/day) as a replacement for 2-acetyl-aminofluorene (2-AAF) in a hepatic 'growth selection' protocol and its ability to alter DNA synthesis in hepatocytes following partial hepatectomy (PH) were determined. tDNT was active in the growth selection protocol but not as effective as 2-AAF. When tDNT was fed (35 mg/kg/day) for 2 wk prior to PH, it had no effect on the kinetics of DNA synthesis following PH. (no Refs)

62. PROMOTING EFFECTS OF 3-AMINO-1,2,4-TRIAZOLE ON THE DEVELOPMENT OF THYROID TUMORS IN RATS TREATED WITH N-BIS(2-HYDROXYPROPYL)NITROSAMINE.

Hiasa Y, Ohshima M, Kitahori Y, Yunoa T, Fujita T, Iwata C
First Dept. Pathology, Nara Medical Univ., Kashihara, Nara, 634, Japan
Carcinogenesis; 3(4):381-384 1982

3-Amino-1,2,4-triazole (AT) promoted the development of thyroid tumors in rats treated with a subeffective dose of N-bis(2-hydroxypropyl)nitrosamine (DHPN) for thyroid tumorigenesis. The incidences of thyroid tumors at the end of the 20-wk experiment were 91% in rats injected sc once a wk for 4 wk with 70 mg DHPN per 100 g body wt and then given diet containing 2,000 ppm AT for 12 wk, 100% in rats injected sc once a wk for 8 wk with 70 mg DHPN per 100 g body wt and then given diet containing 2,000 ppm AT for 12 wk, and 58% in rats injected sc once a wk for 8 wk with 70 mg DHPN per 100 g body wt. Rats only injected sc once a wk for 4 wk with DHPN or only given diet containing AT for 12 wk had no thyroid tumors at the end of the experiment. (Author abstract) (28 Refs)

63. BIPHASIC INFLUENCE OF SELENIUM ON CELL GROWTH AND THE SYNTHESIS OF COLLAGEN IN CULTURED MAMMARY TUMOR CELLS (MEETING ABSTRACT)

Lewko WM, McConnell KP
University of Louisville, Louisville, KY, 40292
Fed Proc; 41(3):623 1982

Selenium is an esstential trace element which has antineoplastic properties. The effects of selenium on cell growth and macromolecular synthesis were analyzed using primary cultures of tumor cells. These cells were prepared from mammary tumors induced in rats by N-nitrosomethylurea. The growth of these tumors has been shown to be dependent upon the synthesis of type IV collagen, the only collagen detectable in cultures of these cells. Other evidence indicated that sodium selenite became incorporated into the collagen of rat skin. The effect of selenium on collagen synthesis was measured by the incorporation of 3H-proline into collagenase-sensitive protein. Lower concentrations of sodium selenite (0.001-0.1ug/ml medium) modestly stimulated cell growth, the incorporation of 3H-thymidine into DNA and the synthesis of type IV collagen. Higher concentrations of sodium selenite (10-100 ug/ml) depressed cell growth, the synthesis of DNA and decreased the synthesis of collagen over that of non-collagen protein. These results suggested that a decrease in collagen synthesis could be responsible for the decreased cell growth and the anti-neoplastic effects of selenium observed in these tumor cells. (no Refs)

64. EFFECT OF MOLYBDENUM ON N-NITROSOSARCOSINE ETHYL ESTER-INDUCED CARCINOGENESIS IN RATS (MEETING ABSTRACT)

Wei HJ, Luo XM, Sproat HF, Yang SP
Department of Chemical Etiology and Carcinogenesis, Cancer Institute, Beijing, China
Fed Proc; 41(3):280 1982

Male weanling rats of the Sprague-Dawley strain were given ad libitum for 19 or 30 weeks a nutritionally adequate diet and deionized drinking water (Groups 1 and 4) or the same diet and 100 ppm W from Na2WO4 (Groups 2 and 5) or 20 ppm Mo (Groups 3 and 6) or 2 ppm Mo (Group 7) from Na2Mo0(4) added to the drinking water. As determined by a catalytic polarographic procedure, the diet contained 0.026 ppm Mo and no detectable Mo in the drinking water. Start from the third week, all the animals in Groups 4-7 were administered via gastric intubation 0.7 g sarcosine ethyl ester and 0.3 g NaN0(2) in 10 ml 0.01 N HCl per kg of body weight twice weekly for 8 consecutive weeks. N-nitrososarcosine ethyl ester (NSEE) is believed to be formed readily under the above condition. At the end of 19 weeks, 80% of the animals in Group 4 developed esophageal and forestomach cancer. This incidence was identical to that of Group 5 and significantly higher than that of Group 6 or Group 7. Similar results were obtained at the end of 30 weeks. No carcinomas were observed in Groups 1-3. (no Refs)

65. CHOLECYSTOKININ INHIBITS NITROSAMINE-INDUCED CARCINOGENESIS (MEETING ABSTRACT)

Johnson FE, LaRegina MC, Martin SA, Bashiti HM
St. Louis University Medical Center, St. Louis, MO
Joint Meeting of the Society of Surgical Oncology and Society of Head and Neck Surgeons, April 18-23, 1982, Marco Island, Florida. The Society of Surgical Oncology and the Society of Head and Neck Surgeons 265 pp., 1982.

Acute administration of cholecystokinin (CCK) has well-known effects on gall bladder contractions and pancreatic-biliary secretion. Recent data indicates that chronic administration of CCK has trophic effects on abdominal viscera, particularly pancreas. In order to determine whether CCK enhances malignant growth as well as growth of normal organs, we administered CCK together with di-isopropanol nitrosamine (DIPN), a carcinogen known to induce pancreatic, hepatic (and other) carcinomas. Two hundred young male Syrian golden hamsters (approx 60 gm) were divided into four groups. Group A (80 animals received DIPN (250 mg/kg) plus CCK (20 U/kg) by weekly subcutaneous injections; Group B (80 animals), DIPN alone; Group C (20 animals), CCK alone; Group D (20 animals), saline. Injections were done for 40 weeks, with animal sacrifice and autopsy at 10, 14, 18, 27, and 40 weeks. Microscopic study of pancreas, liver, heart, lung, brain, spleen small intestine, large intestine, testis, kidney, and stomach was carried out in each animal. Animal weights and visceral weights showed no striking differences between groups. Microscopic examination of the pancreas showed: DIPN induced pancreatic and hepatic carcinomas; CCK administration appeared to prevent their development. The mechanism of this effect is unknown. These results have implications for human carcinogenesis, and some of the implications are testable by currently available methods. (no Refs)

66. THE ACUTE EFFECT ON BETA-SITOSTEROL ON COLONIC EPITHELIAL CELL PROLIFERATION: IMPLICATIONS FOR MNU-INDUCED NEOPLASIA (MEETING ABSTRACT)

Deschner EE, Cohen BI, Raicht RF
Memorial Sloan-Kettering Cancer Center, New York, NY
Cell Tissue Kinet; 15(1):102 1982

The effect of dietary supplementation with beta-sitosterol (0.2% of diet) was followed in Fisher rats after a period of 3 and 7 days feeding. Compared with controls, the number of epithelial cells per crypt column in both plant sterol fed groups was shifted to lower values; moreover, fewer epithelial cells above cell position 12 were engaged in DNA synthesis. Rats treated with MNU (methylnitrosourea) intrarectally (2 mg) while consuming beta-sitosterol demonstrated a reduction in the number of [3H]TdR (thymidine) labelled cells per crypt column from that seen in rodents receiving just the carcinogen. Twenty-six weeks later, MNU-treated rats fed beta-sitosterol showed a significantly decreased colonic tumor incidence (1.3 tumor per tumor-bearing animal vs 2.1 tumor per tumor-bearing animal). This plant sterol which passes through the digestive tract relatively unabsorbed appears to slow colonic epithelial cell proliferation resulting in a reduced expression of neoplastic transformation. (1 Ref)

67. THE EFFECT OF DEPRIVATION OF HEPATIC BLOOD SUPPLY ON THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN RAT (MEETING ABSTRACT)

Wai WI, Wong J, Ong GB
Department of Surgery, University of Hong Kong, Hong Kong, Hong Kong
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

The aim of the experiment is to study the role of portal venous blood and hepatic arterial blood on the growth of hepatocellular carcinoma in rats exposed to carcinogens prior to deprivation of hepatic blood supply. Clinical evidence indicates that shrinkage of tumor may occur after protocaval shunt and hepatic artery ligation. Male Sprague Dawley rats weighing between 250 grams to 300 grams were used. They were given diethylnitrosamine in their drinking water at a dosage of 10 mg/kg/day for 10-16 weeks. Randomly the rats were then assigned to one of the 3 groups for operation under ether anesthesia. Fifty-six rats had end-to-side portocaval shunt, 25 rats had ligation and division of the hepatic artery, 20 rats had a sham operation. At the time of the operation, no tumor was found in the liver. After the operation, carcinogens were stopped and the rats were killed 10-12 weeks later. Fifty per cent of the operated rats survived for a period of 10-12 weeks and were suitable for morphometric assessment; 22 rats in the portocaval shunt group, 15 rats in the hepatic artery ligation group, and 11 rats in the sham operation group. The size of the hepatocellular carcinoma in the shunt group was significantly greater than the tumor in either the hepatic artery ligation group or the sham operation group. There was no difference between the last groups. End-to-side portocaval shunt in rats previously exposed to carcinogen enhances the growth of hepatocellular carcinoma. This may be due to either the diversion of factors in the portal blood which suppress tumor growth, or the atrophy of liver cords after shunting or increased hepatic arterial flow enhances tumor proliferation. (no Refs)

68. CARCINOGENESIS AFTER EXPERIMENTAL VAGOTOMY: A LONG-TERM STUDY IN ANIMALS.

Stegemann B
Chir. Klinik, Allgemeines Krankenhaus fur die Stadt Hagen, Buscheystrasse 15a, D-5800 Hagen, W. Germany
Fortschr Med; 100(13):586-591 1982

Possible carcinogenesis after nonresective gastric surgery was studied. Long-term observations were made of 560 female Wistar rats following surgery. Surgical procedures included truncal vagotomy (TV) with or without pyloroplasty (PP), selective proximal vagotomy (SPV) with or without PP, PP alone, severance of the left gastric artery, TV + PP with duodenogastrostomy in the papillary region (DGP), DGP without TV + PP, TV with resection of the antrum, and control sham operations. Half of all animals received the carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG: 1.48 g/animal) in drinking water for 7 mo beginning 7 wk after surgery; MNNG provided for a comparison of animals with or without exposure to a carcinogenic compound. Overall survival rate was 65.5%; after 390 +-7 days 367 rats were evaluated. Carcinomas were found in 6% of rats that underwent TV + PP wihout MNNG and 8% of rats that underwent SPV + PP without MNNG. Carcinomas were also found in rats that underwent TV + PP with DGP or DGP alone. Cancers developed only at a pH greater than 4 (normal pH was 2-3). Morphological changes noted in test animals included atrophy of the gastric mucosa, achlorhydria, ulceration, and, after drainage surgery, duodenogastric reflux. Results suggest that vagotomy in humans, particularly with drainage procedures, carries a risk of carcinogenesis Careful postoperative surveillance is therefore required for patients undergoing nonresective gastric surgery. (28 Refs) (In GER)

69. INHIBITION OF BLADDER CARCINOMA IN RATS WITH SYNTHETIC RETINOIDS (MEETING ABSTRACT)

Narayana AS, Loening SA, Culp DA
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

We studied the usefulness of 13-cis retinoic acid, a synthetic retinoid, in inhibition of bladder cancer in rats, induced by instillation of methyl nitrosourea intravesically. Control animals received four doses of normal saline intravesically and the experimental animals four instillations of methyl nitrosourea on alternate weeks. The animals were killed periodically from 9th week and all the surviving animals sacrificed at 32 weeks and their bladders examined for incidence of tumors. Epithelial changes were seen from 9th week and gross tumors were found in 90% of the animals at 32 weeks. Control animals developed no tumors. Animals were fed diet containing 13-cis retinoic acid and sacrificed at periodic intervals starting from 9th week and all the surviving animals were sacrificed at the end of 32 weeks. Urinary bladders were examined grossly and histologically for tumors in rats on retinoid containing diet. The analysis of data showed that there is a delay in cellular changes up to 18 weeks in 75% of the animals. The extent and the incidence of tumors is decreased in animals on retinoid containing diet compared to animals eating normal diet. Twenty-six percent of the animals showed no gross tumor but were found to have cellular changes histologically. Forty-five percent of the animals were found to have gross tumors but the area of the bladder that is involved in the malignant process was less than in control animals. The remaining 29% of the

animals were thought to have not benefited by the retinoids. (no Refs)

70. PROTECTIVE EFFECTS OF BLADDER SURFACE GLYCOSAMINOGLYCANS AGAINST CARCINOGENIC AGENTS (MEETING ABSTRACT)

Bodenstab W, Stauffer C, Schmidt JD, Parsons CL
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association Missouri. American Urological Association 254 pp., 1982.

It has been shown in animal models that the bladder surface is lined by a layer of glycosaminoglycans (GAGs) that prevents bacterial adherence and infection. The GAG layer also prevents calcium and proteins from adhering to the bladder surface. We believe that GAG layer acts as a nonspecific barrier between the transitional cells and the environment, protecting them from infection, stone formation and carcinogenesis. To determine whether the GAG layer also blocks the access of carcinogens to the transitional cells we tested the tumorigenic effects of methylnitrosourea (MNU), a complete carcinogen, in 4 groups of rabbits using an in vivo assay that we have described. Group 1 received MNU only; Group 2 underwent removal of the natural GAG layer with HCl followed by treatment with MNU; Group 3 underwent HCl removal of the GAG layer and its replacement with the synthetic analog sodium pentosanpolysulfate (SP54) followed by treatment with MNU; Group 4 received SP54 followed by MNU. All rabbits' bladders were assayed for tumors at 18, 22, 26, 30 and 34 weeks. Group 2 showed the highest incidence of tumors, approximately 55%. Approximately 25% of Group 1 rabbits, 12% of Group 3 rabbits and 6% of Group 4 rabbits developed tumors. The differences between tumor incidence in the groups receiving SP54 before MNU (Groups 3 and 4) and the group receiving MNU after HCl removal of the natural GAG layer (Group 2) were statistically significant, suggesting that SP54 prevented the increased carcinogenic effects of MNU seen in bladders whose natural GAG layer had been removed. (no Refs)

71. TUMOR IMPLANTATION IN THE BLADDER AFTER NONDENUDING INJURY (MEETING ABSTRACT)

Jones KW, Gill WB, Bagley DH
No affiliation given
77th Annual Meeting of the American Urological Association, Inc May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Intraluminal fulguration of the bladder produces a deep injury, denuding the mucosal surface and injuring muscle. N-methyl-N-nitrosourea (MNU), denudes the mucosal surface and causes submucosal edema. Both of these injuries have been shown to increase the rate of tumor implantation significantly over control (saline irrigated) bladders. In contrast intravesical instillation of either 5% Triton X100 or 0.1 NHCl produced a nondenuding bladder injury in which the epithelium was histologically intact. These chemical injuries allowed in vivo crystal adhesion or staining with intravesical dyes, which did not occur in the normal bladder. The rate of tumor implantation after injury with nondenuding agents is compared with that after injury with a denuding agent and with saline irrigated controls. The bladders of C3H/He mice were fulgurated or irrigated with either 0.1 N hydrochloric acid or 5% Triton X100. Fulguration was performed with 4-0 surgical wire insulated with a PE10 catheter placed transurethrally and attached to an electrocautery. Acid or Triton X100 was placed in the bladder through urethral catheters, left in place for two minutes and then washed out with saline. Control animals were catheterized and irrigated with saline. A single cell suspension of FANFT(N[4-(5-nitro-2-furyl)-2 thiazolyl]formamide) induced tumor cells was placed in the bladder. The rate of tumor implantation was 70% in the fulgurated group and 20% in the control group. The implantation rates following 0.1N hydrochloric acid (0%) on 5% Triton X100 (8%) were not significantly different from the controls. Bladder injuries with these nondenuding injuring agents did not increase the tumor implantation rate significantly beyond that of controls, whereas the denuding injury of fulguration increased tumor implantation. (no Refs)

72. EFFECTS OF LEVAMISOLE AND CONTINUOUS BLADDER INSTILLATION OF MITOMYCIN-C ON TRANSPLANTED URINARY BLADDER CANCER (MEETING ABSTRACT)

Koseki K, Akaza H, Hara T, Kobayashi K, Umeda T, Niijima T, Kitagawa H, Iwaguchi T
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

We made the following experimental model systems to study effects of levamisole and continuous bladder instillation of mitomycin C (MMC), using osmotic mini-pump (ALZA, USA), on the transplanted urinary bladder tumor. BBN (4-(butylnitrosoamino)-1-butanol) induced tumor cells were implanted in the bladder wall of inbred ACI/N rats. By osmotic mini-pump, implanted subcutaneously, MMC at the various concentrations were instilled in the bladder. Levamisole, as a immunomodulator, was subcutaneously injected on day 7 after tumor cells implantation at the concentration of 5 mg/kg. Experimental rats were divided into the following 5 groups. 1) Tumor cells implantation only. 2) Tumor cells implantation and levamisole injection. 3) Tumor cells implantation and instillation of saline. 4) Tumor cells implantation and instillation of MMC. 5) Tumor cells implantation, instillation of MMC and levamisole injection. Experimental rats were killed on day 7 and 14 in groups 1), 3) and 4), and on day 14 in groups 2) and 5). Tumor growths were not completely inhibited when 0.34 mg/mini-pump of MMC were instilled to the bladder tumors made by the implantation of 5x10(4) tumor cells. Histologically, cellular degeneration and necrosis were observed on superficial layer of MMC treated groups, however tumor cells were alive in the profunder layer. On group 5), prominent lymphocytic infiltrations in the tumor tissues were observed. (no Refs)

MUTAGENICITY OF NITROSO COMPOUNDS

73. MUTAGENIC ACTIVITY OF THREE ISOMERIC N-NITROSO-N-METHYLAMINO-PYRIDINES TOWARDS ESCHERICHIA COLI K-12 IN IN VITRO AND ANIMAL-MEDIATED ASSAYS.

Kerklaan P, Bouter S, Mohn G
Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, Leiden, The Netherlands
Carcinogenesis; 3(4):415-421 1982

Three isomeric nitrosomethylaminopyridines were tested in vitro and in the host-mediated assay for their activity to induce gene mutations in E coli K-12 strain 343/113. Nitrosodimethylamine (NDMA) and nitrosomethylaniline

(NMA) were also tested. The in vitro mutagenicity tests were performed either without in the presence of various fractions (S-9, microsomes, S-100) of rodent liver homogenates. The in vivo mutagenicity was determined in host-mediated assays, in which the indicator E coli cells were recovered for the liver of treated animals. N-nitro-N-methyl-2-aminopyridine (2-NMPY) and N-nitro-N-methyl-4-aminopyridine (4-NMPY) were activated to mutagenic factors by microsomes, but their mutagenic effect was completely abolished when S-100 was added. N-nitro-N-methyl-3-aminopyridine (3-NMPY) was directly mutagenic for E coli but its mutagenic potential was abolished when S-100 liver fraction was added to the incubation mixtures. NDMA was activated to mutagenic factors with both microsomes and S-9 fractions, whereas NMA could not be shown as mutagenically active under any of the present experimental conditions. It could be shown that the deactivating effect of the S-100 fraction was of non-enzymatic nature, and probably was due to the presence of thiol-containing 'scavenger' molecules in this fraction. In the host-mediated assays, only the 2-isomer among the three exerted a mutagenic affect. The results indicate that the isomers investigated here are mutagenic either directly or upon microsomal activation. The non-carcinogenicity of 3-NMPY and 4-NMPY, and the non-mutagenicity of these compounds in host-mediated assays, is probably the result of very efficient deactivation by cytosolic (thiol-group-containing?) factors. (23 Refs)

74. METABOLIC ASPECTS OF THE COMUTAGENIC ACTION OF NORHARMAN.

Sugimura T, Nagao M, Wakabayashi K
Natl. Cancer Center Res. Inst., Tsukiji, Chuo-Ku, Tokyo, Japan
Adv Exp Med Biol; 136(partB):1011-1025 1982

Microbial mutagenicity tests were conducted using norharman (beta-carboline) in the Ames Salmonella typhimurium assay with strain TA 98. Comutagenicity of norharman with aniline was demonstrated, and linear dose-response curves were obtained with the aniline metabolites phenylhydroxylamine and nitrosobenzene in the presence of 200 ug norharman. Norharman was comutagenic with o-toluidine, but not with m- or p-toluidines. It induced mutagenesis in yellow OB dye, but not red dye number 2, which does not yield either aniline or o-toluidine upon hydrolysis. 3-Aminopyridine and 2-amino-3-methyl-pyridine were mutagenic in the presence of norharman, but eight other aminopyridine derivatives were not. Diphenylnitrosamine (DPhN) and diphenylamine (DPhA) were mutagenic in the presence of norharman and S-9 mix, but not without both added components in the incubation medium. Mutagenicity of DPhN seems to be due to DPhA formed metabolically. Other strains of S typhimurium (TA 1538, TA 1978) showed sensitivity to aniline + norharman, and strains TA 100 and TA 1535 were totally unaffected. A mixture of microsomes + supernatant + NADPH yielded more revertants than microsomes alone, microsomes + NADPH, or supernatant + NADPH. (41 Refs)

75. COMPARATIVE MUTAGENICITY FOR SALMONELLA TYPHIMURIUM OF FOUR NEW NITROSOUREA ANALOGUES: CNCC, RFCNU, RPCNU AND CHLOROZOTOCIN (CZT).

Marzin D, Jasmin C, Imbach JL, Mathe G
Departement de Recherche, Essais Biologiques Stallergenes, 94340 Joinville Le Pont, France
INSERM Symp; 19:165-174 1981

Comparative mutagenicity tests with Salmonella typhimurium were conducted using (chloro-2-ethyl)-1-(ribofuranosyl-1-isopropylidene 2',3'- para-nitro-benzoate-5')-3-nitrosourea (RFCNU), (chloro-2-ethyl)-1-(ribopyranosyl triacetate-2'-3'-4')-3-nitrosourea (RPCNU), chlorozotocin (CZT), and [di(chloro-2-ethyl)-2N nitroso-N-carbamoyl] N,N-cystamine (CNCC). All four compounds had direct mutagenic activity, which was not affected by microsomal extract. Mutagenic activity was not correlated with hematologic toxicity. (16 Refs)

CELLULAR EFFECTS OF NITROSO COMPOUNDS

76. INITIATION OF C3H/10T1/2 CELL TRANSFORMATION BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE AND AFLATOXIN B1.

Boreiko CJ, Ragan DL, Abernethy DJ, Frazelle JH
Chemical Industry Inst. Toxicology, P.O. Box 12137, Research Triangle Park, NC, 27709
Carcinogenesis; 3(4):391-395 1982

The utility of C3H/10T1/2 mouse embryo fibroblasts for the detection of carcinogenic substances has been limited by their apparent insensitivity to the oncogenic effects of direct-acting alkylating agents such as N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and procarcinogens such as aflatoxin B1 (AfB1). Because the process of C3H/10T1/2 transformation can be observed to proceed through discrete stages of initiation and promotion, we have considered the possibility that MNNG and AfB1 may only initiate C3H/10T1/2 transformation. Treatment of asynchronous C3H/10T1/2 cells with MNNG or AfB1 alone generally produced few transformed foci. If MNNG or AfB1 treatment was followed by the exposure of cells to the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA), numerous transformed foci were produced. Phorbol did not enhance transformation by either substance. MNNG and AfB1 thus appear to be initiating agents for transformation. TPA also enhanced the transformation of C3H/10T1/2 cells by low doses of 3-methylcholanthrene (3-MCA), but transformation by high concentrations of 3-MCA was inhibited by the presence of TPA. These studies suggest that the sensitivity of the C3H/10T1/2 transformation system to potential carcinogens can be dramatically heightened if the bioassay is conducted in the presence and absence of TPA. (Author abstract) (37 Refs)

77. IMPROVED TRANSFORMATION OF C3H10T1/2CL8 CELLS BY DIRECT- AND INDIRECT-ACTING CARCINOGENS.

Nesnow S, Garland H, Curtis G
Genetic Toxicology Div., Health Effects Res. Lab., United States Environmental Protection Agency, Research Triangle Park, NC, 27711
Carcinogenesis; 3(4):377-380 1982

Oncogenic transformation of C3H10T1/2CL8 cells was improved by treating the cells 5 days after seeding. Benzo[a]pyrene-induced transformation was increased 3.5-fold by this method, compared with treating the cells 1 day after seeding. N-Methyl-N'-nitro-N-nitrosoguanidine, which does not transform asynchronous cultures of C3H10T1/2CL8 cells when administered 1 day after seeding, produced an average of one focus/dish, with 61% of the dishes exhibiting foci, when administered 5 days after seeding. Propane sultone and aflatoxin B1 also produced marked transformation responses when administered 5 days after seeding. However, 4-

dimethylaminoazobenzene did not induce transformation when administered either 1 day or 5 days after seeding. With all chemicals examined, clonal cytotoxicity was reduced when they were administered 5 days after seeding. These results indicate the utility of this new procedure for the qualitative analysis of the transforming ability of chemicals. (Author abstract) (28 Refs)

78. THE INDUCTION OF SCE AND CHROMOSOMAL ABERRATIONS WITH RELATION TO SPECIFIC BASE METHYLATION OF DNA IN CHINESE HAMSTER CELLS BY N-METHYL-N-NITROSOUREA AND DIMETHYL SULPHATE.

Connell JR, Medcalf AS

Chemical Carcinogenesis Div., Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks HP8 4SP, England

Carcinogenesis; 3(4):385-390 1982

Chinese hamster cells (V79) were treated, either as exponentially proliferating cultures or under conditions where they were density-inhibited, with various doses of the potent carcinogen N-methyl-N-nitrosourea (MNU) or the relatively weak carcinogen dimethylsulfate (DMS). The colony forming ability of these cells and the induced frequencies of sister chromatid exchanges (SCEs) and chromosomal aberrations were assayed. Following the exposure of density-inhibited cells to radio-labeled methylating agents (labeled in the methyl group) these phenomena were related to the levels of 7-methylguanine (7-meGua), O6-methylguanine (O6-meGua) and 3-methyladenine (3-meAde) in the DNA. At equitoxic doses MNU and DMS induced similar frequencies of SCEs and chromosomal aberrations. Since, at equitoxic doses, MNU produces approx 20x more O6-meGua in V79 cell DNA than does DMS, this indicates that the formation of O6-meGua in DNA is not a major cause of SCEs and chromosomal aberrations. DMS-induced SCEs may be mediated via the production of both 3-meAde and 7-meGua in the DNA; these two methylated purines may also be responsible for MNU-induced SCEs. Therefore, no one specific methylated purine was identified as being solely accountable for the formation of SCEs. Also, the repair of lesions in the DNA of non-replication V79 cells leads to a reduction in the SCE frequency on their subsequent release from the density-inhibited state, suggesting that repair is not intimately responsible for their formation. No association was discernable between chromosomal aberrations and any of the three methylated purines studied. (Author abstract) (34 Refs)

79. CHANGES IN RNA SYNTHESIS INDUCED BY N-METHYL-N-NITROSOUREA.

Mironov NM, Prikul' IV, Gorin AI, Tseitlin PI

Lab. Human Tumors, All-Union Cancer Res. Center, Moscow, USSR

Biull Eksp Biol Med; 93(3):25-27 1982

To evaluate the mechanism of the antitumor effect of nitrosoureas, the effect of N-methyl-N-nitrosourea (MNU) on RNA synthesis was studied in isolated nuclei from the liver of Wistar rats. Incubation of chromatin with MNU resulted in the decrease of RNA synthesis. The inhibitory effect of MNU was associated with the shortening of the RNA-transcripts. (10 Refs) (In RUS)

80. DNA ADDUCT FORMATION IN HUMAN AND RAT PANCREATIC EXPLANTS TREATED WITH N-METHYL-N-NITROSOUREA (MNU) (MEETING ABSTRACT)

Friedman S, Parsa I

State University of New York, Downstate Medical Center, Brooklyn, NY, 11203

Fed Proc; 41(3):1548 1982

To evaluate the carcinogenic process in an in vitro model of pancreatic carcinogenesis the early effects of carcinogens on pancreatic explants in organ culture were studied. We have reported that adult human pancreatic explants can be transformed in organ culture by treatment with MNU. Since adduct formation of carcinogens with DNA is believed to play a role in carcinogenesis and is a measure of the reactivity of carcinogens with cellular macromolecules we have examined the reaction products of this alkylating agent with DNA under conditions, in organ culture, which cause the transformation of human pancreatic explants. Explants were exposed to 14C-MNU for 2 hours in a chemically defined medium. Total DNA was extracted by a modification of the method of Marmur and the purines analyzed after hydrolysis of the DNA in 0.1 M HCl at 70 degrees for 30 min by chromatography on Sephadex G-10. The analysis of methylated purine bases formed in the DNA of human pancreas indicates the formation of 1-methyladenine (0.0045 bases/1000 parent base), 3-methyladenine (0.0210), 7-methyladenine (0.0093), 7-methylguanine (0.239) and 06-methylguanine (0.024). MNU is approximately 1/10 as active in alkylating DNA of rat pancreatic explants as it is in alkylating DNA of human pancreas. (no Refs)

81. EUKARYOTIC DNA REPAIR IS BLOCKED AT DIFFERENT STEPS BY INHIBITORS OF DNA TOPOISOMERASES AND OF DNA POLYMERASES ALPHA AND BETA.

Mattern MR, Paone RF, Day RS

Lab. Molecular Carcinogenesis, NCI, NIH, Bethesda, MD, 20205

Biochim Biophys Acta; 697(1):6-13 1982

Inhibitors of (a) DNA topoisomerases (novobiocin and nalidixic acid) and of (b) eukaryotic DNA polymerses alpha (cytosine arabinoside) and beta (dideoxythymidine) blocked different steps of DNA repair, demonstrated by the effects of the inhibitors on the relaxation of supercoiled DNA nucleoids following treatment of human cell cultures with ultraviolet light (1-3 J/m2) or N-methyl-N-nitro-N-nitrosoguanine MNNG (5 or 20 uM) and the subsequent restoration of the supercoiled nucleoids during repair incubation. Changes in the supercoiling of nucleoid DNA were assayed by analysis of their sedimentation profiles in 15-30% neutral sucrose gradients. Inhibition of repair by novobiocin was partially reversible; upon its removal from the culture medium, the nucleoid DNA of repairing cells became relaxed. The DNA polymerse inhibitors allowed the initial relaxation of DNA after treatment of the cells with UV or MNNG but delayed the regeneration of the initial rapidly-sedimenting (supercoiled) nucleoid DNA for 2-4 hr. Dideoxythymidine (1 mM) was more effective than cytosine arabinoside (1 uM) in producing this delay, but neither inhibitor by itself blocked repair permanently. Incubation of ultraviolet-irradiated cells with 1 uM cytosine arabinoside plus 1 mM dideoxythymidine blocked the completion of repair for 24 hr, whereas incubation with 10 uM cytosine arabinoside or 5 mM dideoxythymidine produced only temporary repair delays of 2-4 hr. Thus, it is likely that the two DNA polymerase inhibitors act upon separate targets and that both targets are involved in repair. It is concluded from these and from previous studies that (1) the DNA repair-sensitive target of novobiocin and na-

lidixic acid in vivo is not a DNA polymerase, but, rather, a DNA topoisomerase; (2) this target affects an initial step of DNA repair leading to the relaxation of supercoiled DNA; (3) the DNA polymerization step of repair may involve both alpha- and beta-type DNA polymerases; and (4) in repair one type of DNA polymerase may substitute for another. (Author abstract) (33 Refs)

82. COMPARISON OF THE EFFECTS OF METHYLNITROSOUREA (MNU) ON ORGAN-CULTURED HUMAN AND RAT PANCREAS (MEETING ABSTRACT)

Parsa I, Butt KM
State University of New York Downstate Medical Center, Brooklyn, NY, 11203
Fed Proc; 41(3):379 1982

Organ-cultured adult human pancreas explants prepared from 10 cadaveric donors and in vitro differentiated embryonic rat pancreas were exposed twice a week to 1ug/ml of MNU in a chemically defined medium and cultured for up to 12 weeks. Twice a week rat and human explants were examined by light and electron microscopy to evaluate proliferation, hyperplasia, and carcinoma in ductal epithelium and in cells within the acinar complex. Early non-specific changes, degeneration of organelles, were present in all cell types of both species. Acinar cell necrosis was more prevalent in rat (89%) than in human explants (42%) and peaked by the end of the first week. Ductal cell proliferation and hyperplasia dominated the explant morphology in rat but were also common in human explants. Carcinoma, often in multiple foci, appeared as early as 6 weeks in rat and within 10-12 weeks in human explants. By the end of 12 weeks of treatment human explants showed carcinoma arising in ductal epithelium (20%) and in cells within the acinar complex (40%). More than 50% of rat pancreas explants developed carcinoma. Malignant cells in rat explants appeared to arise from cells devoid of zymogen and to form papillations composed of cells with extensive interdigitation of plasma membranes and an abundance of tono-filaments and tono-fibers, consistent with ductal cell carcinoma. (no Refs)

83. IN VITRO CARCINOGENESIS IN CANINE BLADDER (MEETING ABSTRACT)

Klaunig JE, Constantini MG, Barut BA, Goldblatt PJ
Department of Pathology, Medical College of Ohio, Toledo, OH
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

As part of our overall investigation of mechanisms of bladder carcinogenesis, we have developed methods for establishing primary and secondary cultures of canine bladder urothelial cells. Urinary bladders from adult dogs of mixed breed were removed immediately after exanguination. Four pieces of bladder (0.5 x 0.5 cm) were placed urothelium side up per 60-mm culture dish. Two milliliters of Ham's 151 culture medium were added per dish, and dishes were maintained at 36.5 C in a humidified CO2 incubator. Epithelial cells were seen extending from the explants 2 to 3 days after culture initiation. Within 2 to 3 weeks cells were almost confluent on the culture dish. The inclusion of fetal bovine serum in the medium resulted in the overgrowth of epithelial cultures by fibroblasts. The calcium concentration in the medium had a significant influence on differentiation and growth of primary urothelial cells. A concentration of 1 x 10(-4) M calcium appeared optimal for cell growth and prevention of differentiation. Secondary cultures were initiated by trypsinization of primary cultures. Fetal bovine serum was required in the medium for secondary culture cell growth. DNA repair (measured by inductor of unscheduled DNA synthesis (UDS) was evident in explants, primary, and secondary cultures following exposure to methylnitrosourea, aflatoxin B1, 4-aminobiphenyl, and benzo(a)pyrene. UDS in each compound displayed a linear dose response. Radiolabeled benzo(a)pyrene was metabolized and covalently bound to DNA in bladder explants primary and secondary cultures. (no Refs)

84. THE ROLE OF ISOCYANATE FRAGMENTS IN THE ANTITUMOR ACTIVITY OF CHLOROETHYLNITROSOUREAS (MEETING ABSTRACT)

Gibson NW, Hickman JA
CRC Experimental Chemotherapy Group, Department of Pharmacy, University of Aston, Birmingham B4 7ET, England
Combined Modality Therapy - Clinical and Laboratory Aspects, November 26-27, 1981, London, England British Association for Cancer Research and British Institute of Radiology; :AP.6 1981

The importance of the isocyanate fragment in the in vitro cytotoxicity of chloroethylnitrosoureas (CENUs) has not yet been resolved. We have investigated the cytotoxicity of CENUs and their respective isocyanates (chloroethylisocyanate from BCNU (carmustine), cyclohexylisocyanate from CCNU (lomustine)) to two cell lines which are sensitive to CENUs in vivo (TLX5 lymphoma, L1210 leukemia) and to two which are resistant in vivo (TLX5R lymphoma, L1210R leukemia). The TLX5 lymphoma is resistant in vivo to alkylating agents whereas the L1210 leukemia is highly sensitive. The results indicate that the role of isocyanates in the cytotoxicity of CENUs is dependent upon the cell line under investigation, since a comparison of the concentration required to give a 3 log cell kill against sensitive or resistant lines allows estimation of the selectivity of a cytotoxic fragment. We conclude that isocyanates may be important in the selective toxicity of CENUs to the TLX5 lymphoma, but less so to the L1210 leukemia. (no Refs)

85. DIMINISHED TRANSGLUTAMINASE ACTIVITY IN L1210 MOUSE LYMPHOMA AFTER TREATMENT WITH NITROSOUREAS (MEETING ABSTRACT)

Szabo T, Fesus L, Laki K
Department of Clinical Chemistry, University School of Medicine, Debrecen, Hungary
VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

The cancerostatic activity of nitrosoureas is mainly considered as a result of the modification of nucleic acids via alkylation. Upon decomposition these drugs produce not only alkylating moieties but also carbamoylating isocyanates which in turn bind to cellular proteins thus modifying several enzymes known to play important roles in proliferation. TGase (transglutaminase) is an intracellular enzyme which has recently been implicated in some responses of the living cell such as receptor-mediated endocytosis, lymphocyte mitogenesis etc. BCNU, CCNU and NCNU (carmustine, lomustine, N-chloroethyl-N'-neopenthyl-N-nitrosourea) are potent inhibitors of purified guinea pig TGase. The enzyme activity in the L1210 mouse tumor cells was decreased by 50-60% after in vivo treatment with the usual therapeutic doses of the drugs. No direct cytotoxic effect was observed during one hour incubation of 37C in the presence of 0.1-10.0 mM BCNU, though a time and dose dependent enzyme inhibition has occurred. These results are in accordance with the suggestion of our recently published work

that TGase might play a key role in the escape mechanisms of certain tumors from the host immune system. (no Refs)

IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS

86. IMMUNOLOGICAL PROPERTIES OF IN VITRO PASSAGED CARCINOMAS AND PROPAGATED CLONES FROM DIFFERENT CELL LINES (MEETING ABSTRACT)

Jamasbi RJ, Perkins EH
Antaeus Research Institute, Fayetteville, AR, 72701
Proc Am Assoc Cancer Res; 23:1064 1982

DEN (Diethylnitrosamine)-induced forestomach carcinomas of BALB/c mice are non- or very weakly immunogenic. However, cultured cell lines established from these tumors showed increased immunogenicity, ie, some DEN-induced cell lines lose their tumorigenicity at early passages; others did not lose it up to the 30-50th passages (the highest passages tested). We also observed significant cellular heterogenicity among tumors of the same origin and within the same primary tumor cell line. To determine the degree of cellular heterogeneity among cell lines and if sub-populations of lower tumorigenic cells show selective growth over more tumorigenic cells, we isolated 20 clones from each cell line using early in vitro passages (2-5). Some of the isolated clones failed and some appeared microscopically identical. Generally 3-8 clones from each line grew and demonstrated that different clones show different degrees of tumorigenicity, immunogenicity and invasiveness. The in vitro growth properties of clones isolated from the same primary tumor were also quite different. The more tumorigenic, less immunogenic, metastasizing clones showed significantly lower seeding efficiency, whereas their growth rate and doubling time when they finally attached to the surface of culture dishes were significantly higher than their less tumorigenic, more immunogenic, non-metastasizing counterparts. (no Refs)

87. PREVENTION OF TRANSPLACENTAL CARCINOGENESIS BY THE IMMUNOLOGIC HORMONE LYMPHOTOXIN (MEETING ABSTRACT)

Ransom JH, Evans CH, DiPaolo JA
National Institute of Health, Bethesda, MD, 20205
Fed Proc; 41(3):379 1982

Development of interventive measures to control cancer would be facilitated by monitoring carcinogenesis in vivo with an in vitro assay of morphologic transformation. Syrian hamsters at the 10-11th day of gestation were injected ip with 3 mg diethylnitrosamine (DEN)/100 g. Two days later, fetuses were excised, the fetal cells dissociated and 2000 cells seeded/60 mm dish for colony formation. The frequency of morphologically transformed colonies was determined after 7 days. The mean transformation frequency per cell seeded was 1 x 10(-4) with a 3.6% efficiency of colony formation. Ip injection of an immunologic hormone preparation reduced the transformation frequency by 46%. The preparation was the diafiltered and concentrated lymphokines of phytchemagglutinin stimulated hamster peritoneal leukocytes. It contained 10,000 units of lymphotoxin but no detectable interferon. When DEN exposed cells were x-irradiated with 250 R in vitro and 9000 cells seeded/dish, an increased mean transformation frequency, corrected for x-ray toxicity, of 8.5 x 10(-4) per cell seeded was observed. The DEN + x-ray cocarcinogenic frequency of transformation was reduced 64% by ip injection of the immunologic hormone. This study indicates that immunologic hormones (eg lymphotoxin) can prevent carcinogenesis in vivo and that the in vitro quantitation of transformation provides a means for assessing passively administered and autochthonous effector mechanisms which control carcinogenesis in vivo. (no Refs)

88. NEOANTIGEN EXPRESSION IN CHEMICAL CARCINOGENESIS.

Baldwin RW, Price M
Cancer Res. Campaign Laboratories, Univ. Nottingham, Nottingham, England
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Neoantigens have been found on tumors which were chemically induced by polycyclic hydrocarbons, by aminoazo dyes, by aromatic amines, by alkylnitrosamines, and by hydrazines. Several findings are consistent with the view that tumor-associated antigens on chemically induced tumors are expressed on integral membrane proteins or glycoproteins. Attempts to develop cell-free radioimmunoassays for these antigens have generally been unsuccessful. One of the major problems has been to retain the capacity of the radiolabeled antigens to rebind with antibodies in syngeneic immune sera. The significance of the possible relationships between tumor-associated neoantigens and products of major histocompatibility complex needs to be further evaluated. Oncodevelopmental antigens appear to be associated with numerous types of chemically induced tumors, and thus they should be regarded as valuable potential markers for studying transformation-related events. Three possible pathways leading to neoantigen expression include their appearance as a consequence of early interactions of carcinogen with target cells, their expression which only occurs once the initiated cell is converted to the preneoplastic cell, and their expression at the stage when malignant cell clones develop. (328 Refs)

EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS

89. INTRAGASTRIC ACIDITY, BACTERIA, NITRITE, AND N-NITROSO COMPOUNDS BEFORE, DURING, AND AFTER CIMETIDINE TREATMENT.

Milton-Thompson GJ, Ahmet Z, Barnard J, Brimblecombe RW, Moore PJ, Lightfoot NF, Hunt RH, Bavin PM, Darkin DW, Viney N
Ministry Defence, First Ave. House, High Holborn, London WC1V 5HE, England
Lancet; 1(8281):1091-1095 1982

Eight healthy subjects were studied half-hourly or hourly for 24 hr periods before, during, and after cimetidine treatment. No significant differences in intragastric bacterial counts or bacterial species or in intragastric nitrite or N-nitroso-compound concentrations were found as a result of cimetidine treatment. Bacterial counts and nitrite concentrations tended to increase with pH, but N-nitroso-compound concentrations did not. This study provides no evidence that cimetidine treatment may increase the risk of gastric carcinoma by raising N-nitroso-compound concentrations. (Author abstract) (25 Refs)

90. INHIBITORY EFFECT OF DIFFERENT DIETARY COMPONENTS ON NITROSAMINE FORMATION AND NITRITE LEVELS (MEETING ABSTRACT)

Higgy NA, El-Aaser AA, El-Merzabani MM
Department of Cell Biology, Cairo Cancer Institute, Cairo University, Cairo, Egypt
Fed Proc; 41(3):356 1982

Different vegetables, fruit juices, bread, or yogurt were homogenized and incubated with piperazine and nitrite at pH 4.0 in acetate-HCl buffer. Nitrosamine formation was significantly inhibited as compared to controls. However, with higher levels of nitrite, nitrosamine levels increased. When these dietary homogenates were incubated with nitrite, nitrite levels decreased gradually and then disappeared completely from incubation mixtures. Vegetables like watercress, radishes, lettuce and shikori had high levels of endogenous nitrate, but no nitrite. When these were incubated with nitrite, nitrite levels gradually decreased; then a marked increase occurred after 18 hours of incubation and was attributed to the reduction of the endogenous nitrate. Vegetables and different foodstuffs may have a protective action by inhibiting or interfering with nitrosamine formation. This may be attributed to ascorbic acid, tannins, alpha-tocopherol or other inhibitors of nitrosation, or substances competing with the nitrosatable amine, such as urea and primary amines. This effect may also be due to the disappearance or uptake of nitrite. (no Refs)

91. ORGANIC CONSTITUENTS OF MUTAGENIC SECONDARY EFFLUENTS FROM WASTEWATER TREATMENT PLANTS.

Ellis DD, Jone CM, Larson RA, Schaeffer DJ
(c/o Larson) Inst. Environmental Studies, Environmental Res. Lab., Univ. Illinois, 1000 West Western Ave., Urbana-Champaign, IL, 61801
Arch Environ Contam Toxicol; 11(3):373-382 1982

The tentative identification by gas chromatography-mass spectrometry of 243 organic compounds from 10 municipal and industrial waste effluent sites is reported. Ten of the identified compounds were EPA priority pollutants. Only dimethyl-N-nitrosoamine and ortho-toluidine were known carcinogens or mutagens. Most of the identified compounds, however, have not been tested for carcinogenicity/mutagenicity. (24 Refs)

92. LABORATORY USAGE OF SOME SUSPECT CARCINOGENS (MEETING ABSTRACT)

Dewhurst F
School of Life Sciences, Leicester Polytechnic, Leicester, England
Br J Cancer; 44(2):304 1981

A questionnaire safety survey of British laboratories was carried out through 'Laboratory News' in 1973. A total of 1178 replies was received covering all types of laboratory. Questions were asked concerning the usage of certain types of suspect chemical carcinogen. Less than 1% of replies stated sulphur mustards were used, 1-5% of replies stated nitrogen mustards, ethylene imines, beta propriolactone thioacetamide and nitrosamines were used, while 5-10% stated that asbestos (finely powdered); beryllium, and urethane were used. Between 10 and 20% of replies reported epoxides, thiourea, diazomethane, acetamide, hydrazine, nickel powder, cadmium and arsenic and their compounds. Chromium and its compounds were used by 34% of those replying, while the use of lead and its compounds was reported by 40%. The most commonly reported carcinogens were the solvents chloroform (74% of replies), carbon tetrachloride (66%) and benzene (48%). Weekly or more frequent usage of benzene was reported in 10% of replies, of carbon tetrachloride in 17% and a chloroform in 24%. Evidence in the survey showed serious contamination of the laboratory atmosphere with solvent vapor in about a third of all cases. In about 15%, formaldehyde levels high enough to cause eye irritation were noted. (no Refs)

93. EPIDEMIOLOGY OF CARCINOMA OF THE ESOPHAGUS (MEETING ABSTRACT).

Dorken H
I. Med. Univ. -Klinik, Hamburg, W. Germany
Ninety-eighth Congress of the German Society for Surgery, April 22-25, 1981, Munich, W Germany Deutsche Gesellschaft fur Chirurgie; :A1 1981

There are approx 60 deaths due to (squamous) cancers of the esophagus (1.26% of all tumors) in Hamburg each yr. Mortality figures for the United States (4.3 per 100,000 men and 1.1 per 100,000 women, whites, standardized, 1975) are in keeping with those of most Western countries. There is generally a close correlation with smoking habits and alcoholism. In contrast, in Asia and Africa we find severe 'epidemics' whose max figures approach those for Western total cancer mortality rates, especially in South Africa (Transkei), around the Caspian Sea (Iran, USSR), and in China. In systematic, extensive field studies in all 3 epidemic areas it has been impossible to prove the etiologic influence of environmental factors (mycotoxins, nitrosamines, trace elements, etc). In China, where in certain areas (Linxian, Henan Province) a case of cancer of the esophagus is diagnosed every 8 hr (1,000/yr in a population of 700,000) early diagnosis is being attempted in highly organized campaigns (cytology by means of balloon catheter). Surgical outcome has resulted in a 5 yr survival rate up to 90% as a consequence. Still more astonishing are Chinese Colleague's reports of a corresponding tumor in chickens (squamous cancer of the gullet) which is epidemic in these areas as well. Hence a cancer in man and his hen both in the same house has been discovered (cluster formation). This first epidemiologic discovery of a coincidence of the same cancer in man and his domestic animals must raise the question of viral etiology. (no Refs) (In GER)

94. CURRENT CONCEPTS OF THE ETIOLOGY AND PATHOGENESIS OF LUNG CANCER.

Chaklin AV, Gritsiute LA
No affiliation given
Vopr Onkol; 28(2):3-9 1982

Literature data on the role of smoking and environmental pollutants in the etiology of lung cancer (LC) are reviewed. Epidemiological studies showed the relationship between the smoking and incidence of LC. LC morbidity in 45-64 yr old men increased from 1.4 per 100,000 for nonsmokers to 5.9 for those who smoked 5 cigarettes/day, 13.5 for those who smoked 6-16 cigarettes/day, 29.5 for those who smoked 25-56 cigarettes/day, and 47.4 for those who smoked greater than 56 cigarettes/day. Carcinogenicity of tobacco tar is associated with the presence of polycyclic hydrocarbons, N-nitrosamines, vinyl chloride, phenols, and various co-carcinogens. Recent studies showed the carcinogenic effect of 'passive' smoking. Increased LC morbidity in the regions with intensive chemical industry indicates the co-carcinogenic effect of such air pollutants as sulfur dioxide. Pathogenesis of LC is associated with the history of chronic lung inflammation, tuberculosis, scleroderma, exposure to asbestos, immunologic suppression, and individual activity of aryl hydroxylase. (45 Refs) (In RUS)

95. SMOKING AND CANCER.

Lapis K
No affiliation given
Magy Tud; 89(2):119-127 1982

Epidemiological and etiological relationships between smoking and cancer, especially lung caner, are discussed. The carcinogenic substances occurring in tobacco and cigarette smoke include polycyclic aromatic hydrocarbons, such as benzo(a)pyrene, N-nitrosamines, such as N-nitrosonornicotine, and 210-polonium. Increased incidence of cancer of the larynx, pharynx, lips, oral cavity, tongue, esophagus, urinary bladder, pancreas, and especially lung was observed among smokers compared with nonsmokers. (no Refs) (In HUN)

REVIEWS INCLUDING NITROSO COMPOUNDS

96. HISTORICAL OVERVIEW OF NITROSOUREA DEVELOPMENT.

Goldin A
Div. Cancer Treatment, NCI NIH, Building 37, Room 5E20, Bethesda, MD, 20205
INSERM Symp; 19:3-11 1981

The history of nitrosourea (NU) compounds, including synthetic and natural forms, as agents in the treatment of neoplasia, includes pharmacological development work in several nations. Important differences in mechanisms and therapeutic action have been demonstrated for the various NU analogues. The differences among NU derivatives have permitted manipulation of the host-tumor-drug relationship to improve therapeutic response. (30 Refs)

97. DNA ALKYLATION, CROSSLINKING AND REPAIR.

Kohn KW, Erickson LC, Laurent G
Div. Cancer Treatment, NCI, NIH, Building 37, Room 5D17, Bethesda, MD, 20205
INSERM Symp; 19:33-48 1981

A mechanism of tumor cell killing is described which is based on the inability of cells to repair DNA cross linkages caused by alkylation due to treatment with chloroethylnitrosoureas. DNA alkylation sites, cross linking, strand breaks and alkali-labile lesions, and the role of carbamoylation in the inhibition of DNA repair are discussed. (40 Refs)

98. A MOLECULAR RATIONALE FOR NITROSOUREA INDUCED CYTOTOXICITY.

Tew KD
Lombardi Cancer Center, Div. Medical Oncology, Georgetown Univ., 3800 Reservoir Road, N.W., Washington, DC, 20007
INSERM Symp; 19:61-77 1981

Mechanisms of alkylation and carbamoylation of nuclear macromolecules by chlorozotocin and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, as monitored by 14C-labeling of the chloroethyl group of both drugs, are reviewed. Histone and non-histone proteins, nuclear RNA, and chromatin are discussed as target molecules for alkylation. Cytotoxicity apparently results from interaction with transcriptionally active chromatin and possibly from interaction with the nuclear protein apparatus and interference with DNA association with the nuclear matrix. (20 Refs)

99. ENZYMES INVOLVED IN THE REPAIR OF DNA ALKYLATED BY N-METHYL-N-NITROSOUREA.

Laval J, Pierre J
LA147 C.N.R.S., Institut Gustave Roussy, 94800 Villejulf, France
INSERM Symp; 19:79-84 1981

The removal of the lesions produced by N-methyl-N-nitrosourea (MNU), 3-methyladenine, 7-methylguanine, and apurinic sites, is reported. The study was performed with extracts from Micrococcus luteus, and is indicated that various enzymatic activities in M luteus are able to remove some lesions produced by MNU. These results may have some clinical relevance because nitrosoureas are used as cancer chemotherapeutic agents. It is unknown whether the enzymes extracts from M luteus are capable of handling larger lesions than the methyl one. (21 Refs)

100. MODIFICATION OF DNA AND RNA BASES BY THE NITROSOUREAS.

Ludlum DB, Tong WP
Div. Oncology, Dept. Pharmacology and Experimental Therapy, Albany Medical Coll., Albany, NY, 12208
INSERM Symp; 19:21-31 1981

The nature and significance of nucleic acid modification by the nitrosoureas are reviewed. High pressure liquid chromatographic retention times, uv spectra, and the structures of bases and nucleosides modified by the haloethyl nitrosoureas are given. Evidence for the generation of chloroethylated species from N,N'-bis(2-chloroethyl)-N-nitrosourea and for its reaction with nucleosides to form chloroethyl derivatives is presented. (17 Refs)

101. INHIBITION AND RECOVERY OF DNA AND RNA SYNTHESIS IN NORMAL AND TUMOUR CELLS BY SOME NITROSOUREAS.

Gorbacheva LB, Verovsky VN, Sokolova ES, Kukushkina GV
Inst. Chemical Physics, Acad. Sciences, Vorobievskoe Chausse 2B, 117977 GSP, I Moscow V-334, USSR
INSERM Symp; 19:85-96 1981

The effects of several nitrosourea (NU) derivatives on DNA synthesis by murine bone marrow and gastrointestinal mucosa and the B16 melanoma in vivo, and on RNA synthesis in L1210 leukemia cells in vivo were studied. The compounds suppressed DNA synthesis and timing of recovery in varying degrees according to the agent used. Chromatin transcriptional activity and RNA activity in L1210 cells were also altered by NU treatment. (38 Refs)

102. NEW NITROSOUREAS - THERAPEUTIC AND LONG-TERM TOXIC EFFECTS OF SELECTED COMPOUNDS IN COMPARISON TO ESTABLISHED DRUGS.

Eisenbrand G, Habs M, Zeller WJ, Fiebig H, Berger M, Zelesny O, Schmahl D
Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Postfach 101949, 6900 Heidelberg, W. Germany
INSERM Symp; 19:175-191 1981

Chemotherapy in rodent tumor models, and long-term studies of toxicity and neoplastic induction in rodents were conducted for 23 nitrosourea derivatives. Analogs of established agents with similar clinical cytostatic activity exhibited great differences in long-term toxicity and carcinogenicity, whereas some of the experimental drugs with cytostatic activity superi-

or to better-known agents were less toxic and less carcinogenic. (18 Refs)

103. CHEMICAL CARCINOGENESIS: INTERACTIONS OF CARCINOGENS WITH NUCLEIC ACIDS.

Rajalakshmi S, Prema M, Sarma D
Dept. Pathology, Univ. Toronto, Toronto, Ontario, Canada
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

The nature of modified nucleic acids following interactions with carcinogens is reviewed. Interactions of chemical carcinogens with DNA include covalent interactions such as alkylating agents, nitrosamines and nitrosamides, and noncovalent interactions of both internal and external binding types. Purine-N-oxides and many inorganic metal compounds are known to be carcinogenic. The use of fractionation techniques has revealed that carcinogens exhibit a preferential interaction with some regions of DNA in chromatin. Interactions of chemical carcinogens with RNA have been studied, and alterations in RNA have been attributed to alkylating agents such as nitrosamines and nitrosamides, to urethan, to aromatic amines and amides, and to polycyclic aromatic hydrocarbons. Interactions of carcinogens with nucleic acids exert a profound effect on the structure and synthesis of DNA and RNA, gene expression, and regulation of cellular development. Although the exact mechanism or mechanisms by which DNA damage and repair are involved in carcinogenesis is not completely understood, there is overwhelming evidence indicating a causal relationship between these two processes. (634 Refs)

104. AETIOLOGY OF RENAL TUMOURS (MEETING ABSTRACT)

Pavone-Macaluso M
Institute of Urology and University of Palermo, Palermo, Italy
Renal and Prostatic Tumours, June 2-12, 1981, Erice, Italy NATO Advanced Study Institute; 1981

Our present knowledge of etiology of renal tumors still remains limited. Very few significant contributions have been added to the medical literature since our reviews of 1963 and 1967. This topic can be subdivided into several chapters: etiology of renal cell tumors, etiology of Wilms tumors, etiology of urothelial tumors, of the renal calyces and pelvis, miscellaneous tumors, multiple and bilateral tumors and association with other pathological conditions, and spontaneous renal tumors in the animals and experimental models. Our main interest will be focused to etiology of renal cell carcinoma. An updated review confirms the relatively frequent association of renal cell carcinoma with the von Hippel-Lindau syndrome, whereas Bourneville's tuberous sclerosis is usually associated with renal hamartoma (angiomyolipoma). Sex, race and familiarity also seem to play a role. Viruses, hormones (estrogens), chemical carcinogens (lead, nitrosamines, daunorubicin, etc), irradiation and radioactive substances (thorotrast), cigarette smoking and even natural substances (cyasin) have all been shown to be responsible for cancerogenesis in the kidney, although some of such etiological factors display a strict species specificity. (5 Refs)

105. RISK AND PATHOGENESIS OF STUMP CARCINOMA FOLLOWING GASTRIC SURGERY (MEETING ABSTRACT)

Schlag P
Department of Chirurgie, Universitat Ulm, Steinhovelstrasse 9, D 7900 Ulm, W. Germany
J Cancer Res Clin Oncol; 103(Suppl):A5 1982

The development of a carcinoma in the gastric stump after partial resection for benign disease has been given the term 'carcinoma of the gastric stump.' To rule out the presence of an occult carcinoma at the time of the original gastric resection, a time interval of at least 5 years should have elapsed since operation. The available data indicate that the risk of developing a stump carcinoma steadily increases with time after stomach resection. A review of various studies can not presently decide whether the Billroth I-resected stomach has the same cancer risk as the stomach resected according to the Billroth II-technique. A continuous enterogastric reflux, atrophic stump gastritis and disturbance of the epithelium at the gastroenteral border are considered to be the major factors responsible for carcinogenesis in the operated stomach. One consequence of the treatment of ulcer-disease to reduce the availability of hydrochloric acid is a shift in the bacterial population bringing with it the possibility of intragastric nitrite formation. With high nitrite concentrations the postoperative stomach meets all the conditions needed to favor the production of carcinogenic N-nitroso compounds. The continued formation of such compounds and their metabolites over a long period of time could be a major factor in carcinogenesis of the operated stomach. (no Refs)

106. NITROSAMINES.

Aigner K
Pneumonologische Abteilung, Krankenhaus der Elisabethinen, Fadingerstr. 1, A-4020 Linz-Donau, Austria
Wien Med Wochenschr; 132(71,Suppl):75-79 1982

Health hazards of nitrosamines (NA) are reviewed. NA are formed by the reaction of amines or amides with nitrite or nitrous gases. NA are found in foods, cosmetics, technical oils, pesticides, tobacco, and drugs. Elevated levels of NA have been found in patients with some diseases, including gastric carcinoma. Animal studies have confirmed the carcinogenicity of NA. Further research is required to reduce intake and formation of NA in humans. (17 Refs) (In GER)

AUTHOR INDEX WITH CITATION NUMBERS

Abernethy DJ..... 76
Agemori M..... 33
Ahir S..... 12
Ahmet Z..... 89
Aigner K..... 106
Akaza H..... 72
Allars AJ..... 7
Amberger H..... 49
Ampy FR..... 12
Archer MC..... 3
Aust SD..... 60
Bachmann U..... 49
Bagley DH..... 71
Baldwin RW..... 88
Barnard J..... 89
Barnes SH..... 37
Barut BA..... 83
Bashiti HM..... 65
Bavin PM..... 89
Becker FF..... 25
Becker FF..... 30
Becker FF..... 32
Bedell MA..... 23
Benemanskii V V..... 31
Beniashvili DS..... 50
Berdinskikh NK..... 26
Berdinskikh NK..... 27
Berezov TT..... 29
Berger M..... 102
Bernaert D..... 18
Billings KC..... 23
Bodenstab W..... 70
Boreiko CJ..... 76
Bouter S..... 73
Boyle JM..... 34
Brimblecombe RW..... 89
Britt AL..... 57
Butt KM..... 82
Carter TH..... 48
Castonguay A..... 2
Cater KC..... 19
Chaklin AV..... 94
Chan JY..... 30
Chang D..... 35
Chronister RB..... 53
Chu CK..... 4
Chu YH..... 21
Cohen BI..... 66
Collins MA..... 13
Collins MA..... 14
Connell JR..... 78
Constantini MG..... 83
Coombes RC..... 44
Coombes RC..... 45
Cooper DP..... 20
Cottrell RC..... 13
Cottrell RC..... 14
Cottrell RC..... 7
Culp DA..... 69
Curtis G..... 77
D'Ambrosio S..... 42
D'Ambrosio SM..... 35
D'Ambrosio SM..... 43
Darkin DW..... 89
Dave JR..... 41
Day RS..... 81
Degterev IA..... 36
Dent JG..... 56
Dent JG..... 6
Deschner EE..... 66
Dewhurst F..... 92
DiPaolo JA..... 87
Dorken H..... 93
Durrant L..... 34
Eisenbrand G..... 102
Eisenbrand G..... 11
El-Aaser AA..... 90
El-Merzabani MM..... 90
Ellis DD..... 91
Erickson LC..... 97
Evans CH..... 87
Fesus L..... 85
Fiebig H..... 102
Fong S..... 40
Forsythe L..... 1
Frazelle JH..... 76
Friedman S..... 80
Fujita T..... 62
Fukushima S..... 39
Gandolfi AJ..... 19
Gangolli SD..... 13
Gangolli SD..... 14
Gangolli SD..... 7
Garland H..... 77
Gibson NW..... 84
Gibson-D'Ambros..... 35
Gill WB..... 71
Goldblatt PJ..... 83
Goldin A..... 96
Gombar CT..... 4
Gong M..... 54
Goodman JI..... 60
Gorbacheva LB..... 101
Gorin AI..... 79
Graichen ME..... 56
Gritsiute LA..... 94
Guest D..... 6
Gula EP..... 27
Gurkalo VK..... 59
Gusterson BA..... 44
Gusterson BA..... 45
Habs M..... 102
Habs M..... 49
Habs M..... 55
Hara T..... 72
Harris RA..... 13
Hasegawa R..... 39
Hecht SS..... 10
Heydt G..... 11
Hiasa Y..... 62
Hickman JA..... 84
Hicks RM..... 37
Higgy NA..... 90
Hirose M..... 39
Honma Y..... 38
Huang PH..... 24
Hunt EJ..... 8
Hunt EJ..... 9
Hunt RH..... 89
Imbach JL..... 75
Ito A..... 52
Ito N..... 28
Ito N..... 39
Iwaguchi T..... 72
Iwata C..... 62
Jamasbi RJ..... 86
Jasmin C..... 75
Jensen DE..... 4
Jensen RK..... 60
Jirakulsomchok..... 53
Johnson FE..... 65
Jone CM..... 91
Jones KW..... 71
Kakizoe T..... 38
Kameshita I..... 33
Katul'skii IuN..... 31
Kawachi T..... 38
Kerklaan P..... 73
King EB..... 40
King MM..... 58
Kitagawa H..... 72
Kitahori Y..... 62
Klaunig JE..... 83
Kleihues P..... 46
Knazek RA..... 41
Kobayashi K..... 72
Kohn KW..... 97
Komatsu H..... 38
Koseki K..... 72
Kukushkina GV..... 101
Kunz W..... 15
LaRegina MC..... 65
Lai CN..... 32
Lake BG..... 13
Lake BG..... 14
Lake BG..... 7
Laki K..... 85
Lapeyre JN..... 30
Lapis K..... 95
Larson RA..... 91
Laurent G..... 97
Laval J..... 99
Lee J..... 25
Lenk W..... 17
Leonard TB..... 61
Leong Y..... 35
Leshchenko ME..... 31
Lewko WM..... 63
Lightfoot NF..... 89
Lin D..... 10
Lindamood C..... 23
Liu SC..... 41
Livshits VI..... 26
Loening SA..... 69
Ludlum DB..... 100
Luo XM..... 64
Lutz WK..... 5
Magee PN..... 24

Magee PN 4
Margison GP 20
Margison GP 21
Margison GP 34
Martin SA 65
Maru GB 21
Marzin D 75
Massey RC 1
Mathe G 75
Mattern MR 81
McCay PB 58
McConnell KP 63
McWeeny DJ 1
Medcalf AS 78
Mel'nikova NN 26
Mel'nikova NN 27
Merz R 49
Mhaskar DN 42
Mhaskar DN 43
Millis CD 60
Milton-Thompson 89
Mironov NM 79
Mohla S 12
Mohn G 73
Moore PJ 89
Murasaki G 39
Nagao M 74
Nagase S 38
Naito M 52
Naito Y 52
Nakanishi K 39
Narayana AS 69
Neptun DA 56
Nesnow S 77
Niijima T 72
Nijima T 38
Nishikimi M 33
O'Connor PJ 20
O'Connor PJ 21
Ohshima M 62
Ong GB 67
Oravec C 35
Paone RF 81
Parchman LG 4
Parsa I 80
Parsa I 82
Parsons CL 70
Pavone-Macaluso 104
Penasse W 18
Pereira MA 57
Perkins EH 86
Phillips JC 13
Phillips JC 14
Phillips JC 7
Pierre J 99
Popov KN 36
Popp JA 56
Popp JA 61
Potter DW 16
Prema M 103
Preussmann R 11
Price M 88
Prikul' IV 79
Prusakov VM 31
Raber JM 42
Ragan DL 76
Raicht RF 66
Rajalakshmi S 103
Ramagli LS 25
Ransom JH 87
Reddy J 22
Reed DJ 16
Reiss B 10
Reuter K 43
Rodriguez LV 25
Rowland IR 13
Rowland IR 14
Ruchirawat M 30
Sanina KL 27
Sarma D 103
Sato K 28
Schaeffer DJ 91
Scharmer U 17
Schlag P 105
Schlake W 47
Schmahl D 102
Schmahl D 49
Schmahl D 55
Schmidt JD 70
Schnell SR 6
Schrenk D 15
Schwarz M 15
Scortichini BH 56
Severs NJ 37
Shank RC 8
Shank RC 9
Shizuta Y 33
Siatkin SP 29
Sipes IG 19
Sleight SD 60
Sokolova ES 101
Sproat HF 64
Stauffer C 70
Stegemann B 68
Stewart BW 24
Sugimura T 38
Sugimura T 74
Svoboda DJ 22
Swenberg JA 23
Szabo T 85
Taniguchi T 33
Tennekes HA 15
Tew KD 98
Thompson MB 56
Tong WP 100
Trombetta LD 48
Trosko JE 60
Tseitlin PI 79
Tsuda H 28
Umeda T 72
Van Vunakis H 2
Vanderlaan M 40
Verovsky VN 101
Viney N 89
Volfson NI 59
Wagner I 49
Wakabayashi K 74
Walters DG 7
Wanson JC 18
Wei HJ 64
Wei WI 67
Weisbroth SH 48
Whisler R 43
Williams GM 10
Williams J 45
Williams JC 44
Wong J 67
Wright R 37
Yang SP 64
Yielding KL 53
Yin Z 28
Young PJ 7
Yuasa T 62
Zaikov GE 36
Zelesny O 102
Zeller WJ 102
Zhmareva EN 51
Zimmerman JA 48

Keep Up with the Cancer Literature

Each Month
You Can Receive Abstracts
Covering Your Specialty Area

- This convenient service — called Auto SDI* — is as near as your nearest biomedical library. Discuss your research interests with the librarian who will design an appropriate search strategy.
- Abstracts of the latest published literature are searched automatically each month and those related to your interests are delivered to you on a regular basis.
- The abstracts you receive are selected from more than 4,000 monthly entries made into CANCERLIT — the extensive cancer literature data base of the National Cancer Institute.

Talk With Your Librarian
About the Auto SDI Service TODAY.

*Auto SDI stands for Automatic Selective Dissemination of Information. It is a service provided to you, at minimal cost, by the International Cancer Research Data Bank (ICRDB) — a part of the National Cancer Institute.

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. MICROWAVE HEATING ENHANCES THE MIGRATION OF PLASTICIZERS OUT OF PLASTICS.
Bishop CS, Dye A
East Tennessee State Univ., Johnson City, TN, 37614
J Environ Health; 44(5):231-235 1982

2. DISEASES CAUSED BY EPOXY RESINS.
Konietzko H, Fischer G
Institut fur Arbeits- und Sozialmedizin, Johannes-Gutenberg-Universitat, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany
Zentralbl Arbeitsmed Arbeitsschutz Proph; 32(3):86-91 1982
In GER

3. NITROSAMINES.
Aigner K
Pneumonologische Abteilung, Krankenhaus der Elisabethinen, Fadingerstr. 1, A-4020 Linz-Donau, Austria
Wien Med Wochenschr; 132(71,Suppl):75-79 1982
In GER

4. EXPERIMENTAL TUMORS OF THE PERIPHERAL NERVOUS SYSTEM.
Beniashvili DS
Cancer Res. Center, Tbilisi, USSR
Eksp Onkol; 4(2):12-19 1982
In RUS

5. MUTAGENIC, CARCINOGENIC AND TERATOGENIC EFFECTS OF STYRENE.
Sram RJ, Pohlova H, Topinkova E
Klinika hygieny a epidemiologie, Srobarova 48, 100 42 Prague 10, Czechoslovakia
Prac Lek; 34(2):68-72 1982
In CZE

6. DIETHYLSTILBESTROL: EFFECT OF IN UTERO EXPOSURE.
Burke L
Obstetrics/Gynecology Dept., Harvard Medical Sch., Boston, MA
Curr Probl Obstet Gynecol; 5(2):1-58 1981

7. IN UTERO EXPOSURE TO DIETHYLSTILBESTROL: ADVERSE EFFECTS ON THE REPRODUCTIVE TRACT AND REPRODUCTIVE PERFORMANCE IN MALE AND FEMALE OFFSPRING.
Stillman RJ
Dept. Obstetrics and Gynecology, George Washington Univ. Sch. Medicine and Health Sciences, 2150 Pennsylvania Ave., NW, Washington, DC, 20037
Am J Obstet Gynecol; 142(7):905-921 1982

8. BIOLOGICAL EFFECTS OF MINERAL WOOL.
Petersen R, Ehrhorn H, Mousing K, Sabroe S, Silberschmid M, Venstrup-Nielsen SE
Socialmedicinsk institut, Vesterbro Torv 1-3, DK-8000 Arhus C, Denmark
Ugeskr Laeger; 144(13):971-975 1982
In DAN

DIETARY FACTORS IN CARCINOGENESIS

9. NATURALLY OCCURRING FOOD TOXICANTS: PHENOLIC SUBSTANCES OF PLANT ORIGIN COMMON IN FOODS.
Singleton VL
Dept. Viticulture and Enology, Univ. California, Davis, CA
Adv Food Res; 27:149-242 1981

10. MUTAGENS, CARCINOGENS, AND TUMOR PROMOTERS IN OUR DAILY FOOD.
Sugimura T
Natl. Cancer Res. Inst., Tsukiji, Chuo-ku, Tokyo, Japan
Cancer; 49(10):1970-1984 1982

11. THE BIOLOGICAL EFFECTS OF CARRAGEENAN AND OTHER SULFATED POLYSACCHARIDES WITH PARTICULAR ATTENTION TO IMMUNOLOGICAL AND CARCINOGENIC PROPERTIES.
Larsen B
Kraeftforskningsinstituttet, DK-8000 Arhus C, Denmark
Ugeskr Laeger; 144(12):860-863 1982
In DAN

12. VARIATIONS AMONG SPECIES AND CELL TYPES IN THE EFFECTS OF CAFFEINE ON MUTAGEN-INDUCED CYTOTOXICITY AND POSTREPLICATION REPAIR OF DNA.
Sivak A, Rudenko L, Teague LG
Arthur D. Little, Inc., Cambridge, MA, 02140
Environ Mutagen; 4(2):143-162 1982

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

13. CANCER IN THAILAND: LESSONS FOR CANCER CONTROL.
Miller DG, Somboonsharoen S
Strang Clinic, Preventive Medicine Inst., 55 East 34th St., New York, NY, 10016
Prev Med; 11(2):232-239 1982

14. MEASUREMENT OF CANCER INCIDENCE IN THE UNITED STATES: SOURCES AND USES OF DATA.
Greenberg ER, Colton T, Bagne C
Norris Cotton Cancer Center, Dartmuth-Hitchcock Medical Center, Hanover, NH, 03755
JNCI; 68(5):743-750 1982

15. STUDIES OF CANCER EPIDEMIOLOGY IN THE UNITED STATES OF AMERICA.
Lapin IuE
Moscow, USSR
Feldsher Akush; (2):55-57 1982
In RUS

16. CURRENT CONCEPTS OF THE ETIOLOGY AND PATHOGENESIS OF LUNG CANCER.
Chaklin AV, Gritsiute LA
No affiliation given
Vopr Onkol; 28(2):3-9 1982
In RUS

17. ETIOLOGY OF MOUTH AND LIP TUMORS.
Zabezhinskii MA, Godorozha PD
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Vopr Onkol; 28(2):105-113 1982
In RUS

18. PSYCHIATRIC ASPECTS OF CANCER.
Peterson LG, Popkin MK, Hall RC
P.O. Box 20708, 6431 Fannin, Houston, TX, 77025
Psychosomatics; 22(9):774-793 1981

19. PREDICTIVE IDENTIFICATION OF HYPERSUSCEPTIBLE INDIVIDUALS.
Omenn GS
Dept. Environmental Health, Univ. Washington, Seattle, WA, 98195
JOM; 24(5):369-374 1982

20. CARCINOGENESIS AND CURRENT HYPOTHESIS ON THE TUMOR-HOST INTERACTIONS.
Neiman IM
No affiliation given
Patol Fiziol Eksp Ter; (2):63-70 1981
In RUS

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

21. POLYCHLORINATED BIPHENYLS (PCBS): AN AUSTRALIAN VIEWPOINT ON A GLOBAL PROBLEM.
Richardson BJ, Waid JS
Marine Science Lab., Ministry for Conservation - Victoria, P.O. Box 114, Queenscliff, Victoria 3225, Australia
Search; 13(1/2):17-25 1982

22. SIGNIFICANCE OF ENVIRONMENTAL FACTORS FOR THE DEVELOPMENT OF LEUKEMIA, MYELOMA AND MALIGNANT LYMPHOMA.
Brandt L
Onkologiska kliniken, Lasarettet, Lund, Sweden
Lakartidningen; 79(15):1490-1492 1982
In SWE

23. ENVIRONMENTAL FACTORS AND MALIGNANT HEMATOLOGICAL DISEASES.
Bjorkholm M
Hematologsektionen, Danderyds sjukhus, Danderyd, Sweden
Lakartidningen; 79(15):1457-1459 1982
In SWE

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

24. REGULATION OF GENE EXPRESSION IN NORMAL AND NEOPLASTIC CELLS. A REVIEW.
Hochhauser SJ, Stein GS, Stein JL
Dept. Biochemistry and Molecular Biology, Univ. Florida, Coll. Medicine, Gainsville, FL, 32610
Pathobiol Annu; 11:1-29 1981

25. WHAT ARE ISOZYMES TELLING US ABOUT GENE REGULATION IN CANCER?
Weinhouse S
Fels Res. Inst., Temple Univ. Sch. Medicine, Health Sciences Center, Philadelphia, PA, 19140
JNCI; 68(3):343-349 1982

26. CHANGES IN AMINO ACID AND SUGAR TRANSPORT ACTIVITY ASSOCIATED WITH MALIGNANT TRANSFORMATION.
Nishino H, Inui K
Dept. Biochemistry, Kyoto Prefectural Medical Univ., Kyoto, Japan
Tanpakushitsu Kakusan Koso; 26(7):881-895 1981
In JPN

27. CURRENT VIEWS ON THE NATURE OF MYOEPITHELIAL CELLS AND THEIR ROLE IN THE MORPHOGENESIS OF DYSHORMONAL HYPERPLASIAS AND BREAST TUMORS.
Karelina TV
Central Lab. Pathology, Inst. Human Morphology, Moscow, USSR
Arkh Patol; 44(2):69-73 1982
In RUS

MODIFICATION OF CARCINOGENESIS

28. OVERVIEW: RETINOIDS AND CARCINOGENESIS.
Schramm T, Coutelle R
Zentralinstitut fur Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 52(4):323-336 1982
In GER

29. RETINOIDS, URINARY BLADDER CARCINOGENESIS, AND CHEMOPREVENTION: A REVIEW AND SYNTHESIS.
Lower GM, Kanarek MS
Dept. Veterinary Science, Coll. Agricultural and Life Sciences, Univ. Wisconsin, 1655 Linden Drive, Madison, WI, 53706
Nutr Cancer; 3(2):109-115 1981

30. THE ANTITUMOR POLYSACCHARIDE LENTINAN: AN OVERVIEW.
Chihara G
Natl. Cancer Res. Inst., Tsukiji, Tokyo, Japan
Excerpta Med Int Congr Ser; 576:1-16 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

31. ENDOGENOUS ONCOGENIC TYPE B VIRUSES IN MICE.
Komarova EA, Kriukova IN
All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(2):3-12 1982
In RUS

32. GENETIC INTERACTIONS BETWEEN TUMOR VIRUSES AND HOST CELLS.
Rowe WP
Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
Cancer; 49(10):1958-1962 1982

33. THE PERSISTENCE OF RETROVIRUSES.
Weiss RA
Chester Beatty Res. Inst., Fulham Road, London SW3 6JB, England
Symp Soc Gen Microbiol; 33:267-288 1982

34. HOW DO PAPOVA VIRUSES PERSIST IN THEIR HOSTS?
Griffin BE
Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Symp Soc Gen Microbiol; 33:227-247 1982

35. THE EPSTEIN-BARR VIRUS: HISTORICAL, BIOLOGIC, PATHOLOGIC AND ONCOLOGIC CONSIDERATIONS.
Seemayer TA, Oligny LL, Gartner JG
Dept. Pathology, Montreal Children's Hosp., Montreal, Quebec, Canada
Perspect Pediatr Pathol; 6:1-33 1981

36. KAPOSI'S SARCOMA: WHY A 'HOMOSEXUAL DISEASE'?
Groopman JE, Gottlieb MS
Div. Hematology-Oncology, Univ. California at Los Angeles Sch. Medicine, Los Angeles, CA
Hosp Pract; 17(5):64F-64G,64J,64N,64O,64R,64T 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

37. MAJOR APPROACHES TO THE EXPERIMENTAL STUDY OF LUNG CANCER.
Pliss GB, Turusov VS, Zabezhinskii MA
No affiliation given
Vopr Onkol; 28(2):18-22 1982
In RUS

38. ON THE NECESSITY OF MUTAGENICITY TESTING OF NEW DRUGS.
Bogajewski J, Schoneich J
Zaklad Genetyki Czlowieka, PAN, 60-479 Poznan, Poland
Pol Tyg Lek; 37(2):63-67 1982
In POL

OTHER REVIEWS IN CARCINOGENESIS

39. CANCER - PRINCIPLES AND PRACTICE OF ONCOLOGY.
DeVita VT, Hellman S, Rosenberg SA

NCI, Bethesda, MD
Cancer - Principles and Practice of Oncology. Philadelphia, Lippincott, 1926 pp., 1982.

40. MOVABLE GENETIC ELEMENTS.
Watson JD
Cold Spring Harbor Lab., Box 100, Cold Spring Harbor, NY, 11724
Cold Spring Harbor Symp Quant Biol 45(part 1): 445 pp., 1981.

☆U.S. GOVERNMENT PRINTING OFFICE: 1982-381-847:202

Compilation of Experimental Cancer Therapy Protocol Summaries

April 1982
Sixth Edition

COMPLIMENTARY COPIES NOW AVAILABLE

CONTENT

This document contains summaries of over 1200 open experimental clinical cancer therapy protocols from countries around the world.

Open protocols are arranged in sections according to the specific type of cancer.

Protocols closed in 1981 are listed by title, number, and investigator in a separate section.

INDEXES

Tumor index
Agent/Modality index
Protocol identification number index

Request for 1982 COMPILATION.
(Print Clearly for use as mailing label)

Name: _____

Address: _____

_____

City/State/Zip: _____

Country: _____

Mail to:
Compilation Request
ICRDB Program
National Cancer Institute
Westwood Building Room 10A18
Bethesda, Maryland 20205

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
5285 Port Royal Road
Springfield, Va. 22161

OFFICIAL BUSINESS

Penalty for Private Use, $300

PRINTED MATTER

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF COMMERCE
COM-211

THIRD CLASS
BULK RATE

U.S.MAIL

CK-01

CANCERGRAMS are distributed for the International Cancer Research Data Bank (ICRDB) by the National Technical Information Service (NTIS). CANCERGRAMS are available from NTIS on a standing order basis at $2 each for North American Continent addressees and $3 each for other addressees. An NTIS deposit account is required. For a list of subject categories or other information, please write to:

Subscription Section
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161

NOTICE OF MAILING CHANGE

☐ Check here if you wish to discontinue receiving this publication.

☐ Check here if your address has changed and you wish to continue receiving this publication. (Be sure to furnish your complete address including zip code.)

Tear off cover with address label still affixed and send to:

Computer Support Center
ICRDB Program
IIT Research Institute
10 West 35th Street
Chicago IL. 60616

CK 01/82/11

NCI/ICRDB/CK01 82/11

PB82-935111

ICRDB CANCERGRAM

CHEMICAL CARCINOGENESIS

Nitroso Compounds

SERIES CK01 No. 82/11 NOVEMBER, 1982

This Cancergram is a service of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM of the U.S. National Cancer Institute. Every few weeks, an updated Cancergram containing abstracts of selected cancer-related articles recently published in more than 3000 journals, and dealing with the topic indicated by the above title, is sent to researchers working in this area. These researchers are identified on the basis of the description of their current research project that has been submitted to the ICRDB Program, directly or via granting agencies.

This Cancergram is prepared by the Cancer Information Dissemination and Analysis Center (CIDAC) for Carcinogenesis Information. ***If this Cancergram is useful and valuable, please send your comments to the CIDAC address below, since future editions depend on user satisfaction and user needs:***

CIDAC FOR CARCINOGENESIS INFORMATION
SCIENCE INFORMATION SERVICES
FRANKLIN INSTITUTE RESEARCH LABORATORIES
20TH AND RACE STREETS
PHILADELPHIA, PA 19103

NEWARK PUBLIC LIBRARY

NOV 18 1982

U. S. GOVT. PUBS
DEPOSITORY 376

In this issue:

- METABOLISM OF NITROSO COMPOUNDS..... 1-7
- INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS..... 8-24
- MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS..... 25-32
- MUTAGENICITY OF NITROSO COMPOUNDS..... 33-56
- CELLULAR EFFECTS OF NITROSO COMPOUNDS..... 57-63
- TRANSPLACENTAL EFFECTS OF NITROSO COMPOUNDS..... 64-65
- IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS..... 66-68
- EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS..... 69-75
- REVIEWS INCLUDING NITROSO COMPOUNDS..... 76-79

METABOLISM OF NITROSO COMPOUNDS

1. GUT REACTIONS OF RADIOACTIVE NITRITE AFTER INTRATRACHEAL ADMINISTRATION IN MICE.

Thayer JR, Chasko JH, Swartz LA, Parks NJ
(c/o Parks) Lab. Energy-Related Health Res., Univ. California, Davis, CA, 95616
Science; 217(4555):151-153 1982

Intratracheal administration to mice of radioactive nitrite labeled with nitrogen-13 (13NO2-) (half-life, 9.96 minutes) in dosages that do not cause pharmacological perturbation reveals that oxidative and reductive reactions occur in different organs. Oxidation of 13NO2-to radioactive nitrate (13NO3-) predominates in the blood and liver. Reduction of 13NO2-occurs in those mice that harbor intestinal microflora; this reduction does not occur in germ-free mice. The intestinal reduction products include ammonium, glutamate, glutamine, and urea. With a detection limit of about 0.01% of the instilled nitrogen-13, no labeled nitrosamines were detected within 30 minutes. Reduced nitrogen-13 is transported out of the intestine into the circulatory system and appears in the urine along with 13NO3-. The biological half-period for 13NO2-destruction is

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3/73/2:

about 7 minutes, and both oxidation and reduction products are formed. (Author abstract) (37 Refs)

2. ESOPHAGEAL AND HEPATIC MICROSOMAL METABOLISM OF N-NITROSOMETHYLBENZYLAMINE AND N-NITROSODIMETHYLAMINE IN THE RAT.

Labuc GE, Archer MC
(c/o Archer) Dept. Medical Biophysics, Univ. Toronto, Ontario Cancer Inst., Toronto, Ontario, M4X 1K9, Canada
Cancer Res; 42(8):3181-3186 1982

The metabolism of the rat esophageal carcinogen N-nitrosomethylbenzylamine (NMBzA) was studied using microsomes prepared from liver and esophageal mucosa of untreated male Sprague-Dawley rats. NMBzA was extensively metabolized to benzaldehyde, benzyl alcohol, and formaldehyde by hepatic microsomes. The rate of metabolism at the benzyl moiety was 10-fold higher than that at the methyl moiety. Mucosal microsomes metabolized NMBzA to benzaldehyde and formaldehyde at rates one-fifth and one-sixtieth of those in the liver, respectively; benzyl alcohol formation was undetectable. Esophageal metabolism of NMBzA was exclusively located in the mucosa, preferentially in the microsomal fraction, was reduced nicotinamide adenine dinucleotide phosphate dependent, and was inhibited by CO and 2-diethylaminoethyl-2,2-diphenylvalerate. A low level of cytochrome P-450 was detected in the mucosal microsomes. Whereas hepatic metabolism of NMBzA was inducible by phenobarbitone pretreatment, mucosal metabolism was not altered by either phenobarbitone or 3-methylcholanthrene pretreatment. The hepatocarcinogen N-nitrosodimethylamine was extensively metabolized by hepatic microsomes to formaldehyde, but demethylation was not detected in the microsomes from esophageal mucosa, a nontarget tissue. The results indicate that rat esophageal mucosa contains an enzyme system which metabolized NMBzA at a high rate and exhibits properties typical of cytochrome P-450. This enzyme may play a role in determining which compounds induce tumors in rat esophagus. (Author abstract) (26 Refs)

3. MECHANISM OF ESOPHAGEAL TUMOR INDUCTION IN RATS BY N-NITROSOMETHYLBENZYLAMINE AND ITS RING-METHYLATED ANALOG N-NITROSOMETHYL(4-METHYLBENZYL)AMINE.

Hodgson RM, Schweinsberg F, Wiessler M, Kleihues P
(c/o Kleihues), Pathologisches Institut, Albertstrasse 19, 78 Freiburg, W. Germany
Cancer Res; 42(7):2836-2840 1982

The metabolism of the esophageal carcinogen N-nitrosomethylamine (MBN) and its ring-methylated analog N-nitrosomethyl(4-methylbenzyl)amine (4-MeMBN) was investigated in male Wistar rats. When given in drinking water, both compounds have been shown to induce a high incidence of esophageal carcinomas but, after systemic administration of equimolar doses, 4-MeMBN is considerably less toxic and carcinogenic than in MBN. The data indicate that the lower toxicity and carcinogenicity of 4-MeMBN after systemic administration are due to the rapid formation (mainly in the liver) and excretion via the urine of its benzoic acid derivative. The strong carcinogenic effect of po 4-MeMBN can be explained by direct uptake from the drinking water into the esophageal mucosa. Following a single iv injection of [methylene-14C]MBN and 4-Me[methylene-14C]MBN, no benzylated bases were detectable in rat tissues. This indicates that the bioactivation of these compounds is initiated predominantly by hydroxylation at the methylene bridge leading to a methylating rather than a benzylating intermediate as the ultimate carcinogen. (14 Refs)

4. N-PROPYLDIAZONIUM ION ALKYLATES O6 OF GUANINE WITH REARRANGEMENT, BUT ALKYLATES N7 WITHOUT REARRANGEMENT.

Scribner JD, Ford GP
Pacific Northwest Res. Foundation, 1124 Columbia St., Seattle, WA, 98104
Cancer Lett; 16(1):51-56 1982

The product distribution obtained from the reaction of guanine with the n-propyldiazonium ion was investigated. In both in vitro experiments using guanosine and in vivo experiments in which male Sprague-Dawley rats received an injection of 0.3 millimole 3H-di-n-propylnitrosoamine and RNA extracted 12 hr later, alkylation of 7-position of guanine proceeded primarily without rearrangement. Because of the ready rearrangement of the presumed n-propyl cation to the isopropyl cation, alkylation products of n-propylnitrosourea should have been isopropyl derivatives. Most O6-alkylation products were the result of n-propyl cation rearrangement, ie, O6-isopropylguanosine. These results suggest that a new view of alkylation in aqueous media must be developed, and that classical approaches for describing reactivity of alkylating agents are inadequate. (10 Refs)

5. A NON-INVASIVE METHOD FOR THE STUDY OF HEPATIC DRUG METABOLISM IN RODENTS: ANTINEOPLASTIC DRUG EFFECTS ON ANTIPYRINE METABOLISM IN MICE.

Wilson VL, Larson RE, Moldowan MJ
(c/o Moldowan) Sch. Pharmacy, Oregon State Univ., Corvallis, OR, 97331
Chem Biol Interact; 40(2):159-168 1982

A rapid, sensitive and simple high pressure liquid chromatography (HPLC) method is described for the direct analysis of antipyrine in saliva. The detection limit was found to be 1.0 ng/ml of sample, lower than any previously reported method. Accuracy and precision were maintained with as little as 0.5 ul of saliva. Thus the rate of elimination of antipyrine has been monitored non-invasively in rats and for the first time in mice. The antipyrine half-life was found to be 28.9 +-4.0 (SEM) min and 111 +-20 min in mice and rats, respectively. In mice single ip doses of 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU) (30 mg/kg) produced increases in antipyrine half-life, up to 28 days post-treatment. The max effect of BCNU was observed on day 7 with an antipyrine half-life of 74.4 +-15.7 min. Phenobarbital induction lowered the antipyrene half life controls to 12.6 +-1.2 min. An enhanced inductive effect was observed in BCNU-treated mice: BCNU-treated, phenobarbital-induced mice displayed a half-life for antipyrine of 7.4 +-0.6 min on day 21 post BCNU dose. These effects could not be attributed to changes in absorption of antipyrine in BCNU-treated mice. (Author abstract) (25 Refs)

6. STIMULATION OF CHOLINE AND METHIONINE INCORPORATION INTO LIVER PHOSPHOLIPIDS OF RATS FOLLOWING CHRONIC TREATMENT WITH DIETHYLNITROSAMINE.

Raj HG, Poirier LA
Dept. Biochemistry, Vallabhbhai Patel Chest Inst., Univ. Delhi, Delhi 110 007, India
IRCS Med Sci [Cancer]; 9(10):899-900 1981

The relation of the methyl deficiency previously associated with chronic diethylnitrosamine (DENA) to an increased requirement for methyl groups for phospholipid synthesis was in-

vestigated in male Sprague-Dawley rats. DENA (100 ppm in drinking water for 3 wk) resulted in a significant increase in the incorporation of choline-methyl-14C into phosphatidylcholine in the livers, a 39% increase in the incorporation of r ethionine-methyl-14C into hepatic phosphatidylcholine, a significant decrease in incorporation of ethanolamine into phosphatidylethanolamine, and an increase in the incorporation of formate into phosphatidylserine. Neoplastic changes were seen in the livers of DENA-treated rats. (7 Refs)

7. A NEW CLASS OF NITROSOUREAS. III. SYNTHESIS AND ANTITUMOR ACTIVITY OF 3,3-DISUBSTITUTED-1-(2-CHLOROETHYL)-1-NITROSOUREAS HAVING AN ARABINOPYRANOSYL, XYLOPYRANOSYL OR RIBOPYRANOSYL MOIETY.

Morikawa T, Ozeki M, Umino N, Kawamori M, Arai Y, Tsujihara K (c/o Tsujihara) Res. Laboratories, Tanabe Seiyaku Co., Ltd., 2-2-50 Kawagishi, Toda-shi, Saitama 335, Japan
Chem Pharm Bull (Tokyo); 30(2):534-543 1982

Synthesis and antitumor activity of a new class of 3,3-disubstituted-1-(2-chloroethyl)-1-nitrosoureas bearing an aldopentose moiety such as L- or D-arabinose, D-xylose, or D-ribose are described. The glycopyranosylnitrosoureas were tested for antitumor activity against leukemia L1210 and Ehrlich ascites carcinoma by methods previously described. These nitrosoureas appear to be activated nonenzymatically by attack of the hydroxyl group of the sugar moiety on the carbonyl group to give the cyclic carbamate and had large therapeutic ratios against leukemia L1210 and Ehrlich ascites carcinoma. (7 Refs)

INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS

8. COMPARATIVE TUMOR INITIATING ACTIVITIES OF N-NITROSOMETHYLBENZYLAMINE AND N-NITROSODIMETHYLAMINE IN RAT LIVER.

Labuc GE, Archer MC (c/o Archer) Dept. Medical Biophysics, Univ. Toronto, Ontario Cancer Inst., 500 Sherbourne St., Toronto M4X 1K9, Canada
Carcinogenesis; 3(5):519-523 1982

The tumor initiating activities of nitrosomethylbenzylamine (NMBzA), an esophageal carcinogen, and nitrosodimethylamine (NDMA), a hepatocarcinogen, were compared in rat liver using modifications of the initiation assays of Tsuda et al and Pitot et al. Equimolar doses of NMBzA or NDMA (33.5 umol/kg) were injected ip into male Sprague-Dawley rats 18 hr after partial hepatectomy. Following selection, foci of preneoplastic hepatocytes were detected by histochemical staining for gamma-glutamyltranspeptidase. Nitrosomethylamylamine (NMAmA, 115 umol/kg), also an esophageal carcinogen, was tested in the assay of Tsuda et al, and nitrosodimethylamine (NDEA, 33.5 umol/kg), a hepatic and esophageal carcinogen, was tested in the assay of Pitot et al. Both NDMA and NDEA induced significant increases in the number of preneoplastic foci above background. In contrast, neither NMBzA nor NMAmA increased the number of foci above background. Microsomes from regenerating liver had a lower capacity to metabolize both NDMA and NMBzA compared to microsomes from intact liver, but the decrease in activity was similar for both compounds. Neither NDMA nor NMBzA significantly inhibited the first wave of DNA synthesis in vivo in the regenerating liver. The results demonstrate that in contrast to NDMA and NDEA, NMBzA and NMAmA lack tumor initiating activity in the liver. (Author abstract) (37 Refs)

9. COMPARATIVE CARCINOGENICITY OF O-TOLUIDINE HYDROCHLORIDE AND O-NITROSOTOLUENE IN F-344 RATS.

Hecht SS, El-Bayoumy K, Rivenson A, Fiala E

Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Cancer Lett; 16(1):103-108 1982

The carcinogenicity of o-toluidine hydrochloride (TOL) and o-nitrosotoluene (NTOL) in F-344 rats was evaluated. Mean weights were somewhat lower in the TOL and NTOL groups than in the control group. The mean daily doses of TOL and of NTOL (administered in the diet) were 0.062 g and 0.051 g, respectively. Food consumption was slightly less in the treated animals than in the animals fed the control diet. NTOL was significantly more effective than TOL in inducing hepatomas and bladder papillomas but was less active in the induction of mammary fibroadenomas. Both compounds induced significant numbers of fibromas of the skin and spleen as well as peritoneal tumors. The sc tumors were fibromas or mammary fibroadenomas. The peritoneal tumors were mesotheliomas and low grade spindle cell sarcomas. All invaded deeply into various abdominal organs and the muscular wall of the cavity. Most liver tumors were highly malignant hepatocarcinomas. Two rats displayed enormous multiple metastases of hepatoma tissue to the lungs. Bladder and kidney tumors were of the usual transitional epithelium type. These results suggest that N-oxidation is important in the induction of bladder and liver tumors, while other metabolic conversions may play a role in the induction of other tumor types observed. (15 Refs)

10. DIMETHYLNITROSAMINE ADDUCTS EXCRETED IN RAT URINE.

Hemminki K, Vainio H

Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, SF-00290 Helsinki 29, Finland
Adv Exp Med Biol; 136B:1149-1156 1982

Urinary excretion products found after the administration of dimethylnitrosamine (DMN) to Wistar rats were detected with an assay involving nucleic acids and protein. Rats received 25 uCi of 14C-DMN and urine was collected daily. Three main peaks of radioactivity were detected in each urine sample. The peaks were then analyzed with thin layer and high pressure chromatography, a muBondaPak C18 column, and dissociation constants and relative turnover rates were determined. Fraction I was thought to consist of S-methylcysteine; its approx half-life was 1.7 days, slightly shorter than that of methylated proteins in vivo. Urinary S-methylcysteine may be derived from the degradation products of methylated proteins and/or glutathione. Fraction II could not be identified; its properties suggested that it was probably not a methylated degradation product of nucleic acids or protein. Fraction III was identified as 7-methylguanine, with an approx half-life of 2.4 days. 7-Methylguanine may be derived from methylated RNA and DNA. These findings illustrate the usefulness of the study of urinary adducts of carcinogens for monitoring a known chemical exposure and providing information about an unknown exposure. (13 Refs)

11. INFLUENCE OF AGE ON HEPATOCARCINOGENESIS IN RATS INGESTING DIETHYLNITROSAMINE.

Mochizuki Y, Furukawa K
Dept. Pathology, Cancer Res. Inst., Sapporo Medical Coll., Sapporo 060, Japan
Tumor Res (Sapporo); 16:19-28 1981

The effect of increasing age on the incidence of hepatocellular carcinoma induced in male Fischer rats by diethylnitrosamine (DEN) was investigated. The av amounts of daily intake of DEN per rat in Group I (3 mo old), II (6 mo old), III (9 mo old) and IV (12 mo old) were 0.77, 1.16, 0.83, and 1.03 mg, and total amounts were 53.6, 81.0, 57.8, and 72.2 mg, respectively. All rats in Group I had liver tumors larger than 5 mm in diameter. The av number of tumors larger than 5 mm in diameter in Group I was 8.30. In Group II, 75% of rats had tumors larger than 5 mm, the av number of which was 2.25 per rat. In Group III, 60% of rats had tumors larger than 5 mm. Av number of tumors per rat was 1.80. In Group IV, 63% of rats had tumors larger than 5 mm, the av number of which was 2.00 per rat. Differences were statistically different between Group I and Group II-IV. The mechanisms by which older animals are more refractory to DEN induction are discussed. (27 Refs)

12. LOCALIZATION AND BINDING OF N'-NITROSONORNICOTINE METABOLITES IN THE NASAL REGION AND IN SOME OTHER TISSUES OF SPRAGUE-DAWLEY RATS.

Lofberg B, Brittebo EV, Tjaive H
(c/o Brittebo) Faculty Veterinary Medicine, The Swedish Univ. Agricultural Sciences, Box 573, S-751 23 Uppsala, Sweden
Cancer Res; 42(7):2877-2883 1982

Microautoradiography of the nasal region of the Sprague-Dawley rat after N'-[14C]nitrosonornicotine administration showed the highest labeling in the subepithelial glands (Bowman's glands) beneath the olfactory epithelium. A lower but distinct radioactivity was also present in the olfactory and respiratory epithelia, covering various parts of the nasal cavity. An exception was the vomeronasal organ, in which neither the olfactory nor the respiratory epithelium was labeled. Determination of the radioactivity bound to DNA, RNA, and proteins isolated from the nasal mucosa and the liver after N'-[14C]nitrosonornicotine administration showed a higher binding of radioactivity to protein and RNA in the nasal mucosa than in the liver, whereas the binding to DNA was somewhat higher in the liver than in the nasal mucosa. Estimations of tissue-bound and non-tissue-bound radioactivity in various tissues of rats given N'-[14C]nitrosonornicotine showed high levels of nonbound radioactivity in the preputial, submaxillary, and Zymbal's glands, whereas a considerable level of tissue-bound radioactivity was present in the nasal mucosa and the liver and also in the esophagus, trachea, and lung. Microautoradiography of the latter tissues showed that this labeling was localized to the epithelia of the esophagus, trachea, and bronchial tree, respectively. (Author abstract) (12 Refs)

13. LABELLING IN CELLS OF THE NASAL CAVITY OF HAMSTERS TREATED WITH TRITIATED N-NITROSODIETHYLAMINE.

Reznik-Schuller HM
Chemical Carcinogenesis Program, NCI-Frederick Cancer Res. Facility, Frederick, MD, 21701
Cancer Lett; 16(1):109-114 1982

The site of binding of N-nitrosodiethylamine (DEN) or its metabolites was investigated using high resolution light microscopic autoradiography in the nasal cavity of male Syrian golden hamsters. Labeling in the atrioturbinals, which are coated with squamous epithelium, was extremely low and did not exceed background levels. In maxillo- and nasoturbinals, which are coated with respiratory epithelium and have abundant submucous glands, autoradiographic grains were concentrated in specific cell types. In the turbinal epithelia the cytoplasm of mucosous cells showed the most intense labeling, with no preferred localization of radioactivity within the cytoplasm observed. Ciliated cells contained only a few grains. Basal cells demonstrated slight labeling in the nuclei, with no cytoplasmic labeling. High levels of labeling were observed in the cytoplasm of submucous glands, with little or no labeling over nuclei. Distribution of grains within the cytoplasm appeared to be random. Most grains were concentrated in the submucous glands in the endoturbinal region, with olfactory epithelium being only slightly labeled. Olfactory sensory cells remained unlabeled, and labeling in the cytoplasm of sustentacular cells and in the nuclei of basal cells was low. Only epithelial labeling was evident in studied tissue sections. (15 Refs)

14. TUMORIGENESIS AT A PREDETERMINED ORAL SITE AFTER ONE INTRAPERITONEAL INJECTION OF N-NITROSO-N-METHYLUREA.

Konstantinidis A, Smulow JB, Sonnenschein C
Dept. Stomatology, Dental Sch., Univ. Thessaloniki, Thessaloniki, Greece
Science; 216(4551):1235-1237 1982

Tumors in the soft tissues of the oral cavity of rats developed at predetermined sites as a result of a combination of an intraperitoneal injection of a direct-acting carcinogen, N-nitroso-N-methylurea, and a continuous irritation of the buccal mucosa by a stainless steel wire. The incidence of histologically malignant tumors was significantly higher in the irritated area than in any other area of the body. These results constitute evidence for a carcinogenic mechanism whereby the cells that develop into tumors may require the promotional effect of a nonspecific, nonmutagenic stimulus. (Author abstract) (26 Refs)

15. HISTOCHEMICAL ELUCIDATION OF HAMSTER PANCREATIC CARCINOGENESIS INDUCED BY N-NITROSO-BIS(2-HYDROXYPROPYL) AMINE.

Miyazaki K, Takasan H, Hamashima Y
1st Dept. Surgery, Faculty Medicine, Kyoto Univ., Sakyo-ku, Kyoto 606, Japan
Nippon Geka Hokan; 51(1):3-13 1982

Hamster pancreatic carcinogenesis induced by 500 mg/kg/wk sc N-nitroso-bis(hydroxypropyl) amine (DHPN) was studied in 20 outbred 8-wk-old Syrian golden hamsters. Pathological and histological changes were observed 4-27 wk after the induction of carcinogenesis. The most frequent change observed was multilayer hyperplasia of intralobular ductules. After 22 wk adenocarcinomas were observed. The distribution and intensity of enzyme activity is listed. In adenocarcinomas, strong activities of alkaline phosphatase, succinate dehydrogenase, lactate dehydrogenase (LDH), glucose-6-phosphatase (G-6-PD), and NADH-tetrazolium reductase were observed. Moderate activity of LDH and G-6-PD was proved in the epithelium of adenocarcinomas. In the control group, 3H-thymidine uptake (TU) was observed in all tissues components. TU of the acinar cells, interlobular ductules (ILD), and main pancreatic ducts was greater than that of islet cells. After DHPN administration, a significant increase of TU was observed. No TU in-

crease was observed in islet cells. TU of flat epithelial and hypertrophic multiplications and multilayer hyperplasia of ILD was greater than in controls. TU of hypertrophic epithelial multiplications was significantly greater than that of flat. TU of adenocarcinoma epithelium was significantly greater than that of other lesion and normal tissue components. The differences of serum ribonuclease and amylase activity between DHPN-treated and control animals are presented. (17 Refs)

16. ULTRASTRUCTURAL ANALYSIS OF PANCREATIC CARCINOGENESIS. V. CHANGES IN DIFFERENTIATION OF ACINAR CELLS DURING CHRONIC TREATMENT WITH N-NITROSO-BIS(2-HYDROXYPROPYL)AMINE.

Flaks B, Moore MA, Flaks A
Dept. Pathology, Univ. Bristol Medical Sch., Univ. Walk, Bristol, England
Carcinogenesis; 3(5):485-498 1982

An electron microscope study was carried out on changes in the pancreatic acinar tissues of male Syrian hamsters during the course of induction of pancreatic neoplasia by lifetime weekly injections of N-nitroso-bis(2-hydroxypropyl)amine (BHP). The dominant process observed was a loss of differentiation of the acinar cells, leading to the development of a new population of cells that closely resemble centro-acinar or ductular cells. During this process, the original centro-acinar and ductular cells appear to be relatively unaffected by exposure to BHP. Thus, acinar cell dedifferentiation appears, in this experimental model, to be an important preliminary stage in neoplastic development. It is argued that these findings may have implications for the histogenesis of human pancreatic adenocarcinoma, considered hitherto to be ductal in origin. (Author abstract) (52 Refs)

17. HISTOGENESIS OF BILE DUCT CARCINOMA ARISING IN OPISTHORCHIS VIVERRINI INFECTED HAMSTERS GIVEN A SINGLE ORAL DOSE OF DIMETHYLNITROSAMINE (MEETING ABSTRACT)

Flavell DJ
Department of Medical Helminthology, London School of Hygiene and Tropical Medicine, St. Albans, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh Scotland. British Association for Cancer Research 78 pp., 1982.

Intrahepatic bile duct carcinoma appears to be associated with Opisthorchis viverrini infection in man. Long term superinfections in hamsters of up to 20 months duration do not result in hepatic tumors. Thamavit et al however produced a 100% incidence of cholangiocarcinomas by administering 0.0025% dimethylnitrosamine (DMN) to O viverrini infected hamsters. In this study a dose of DMN expected to induce a low incidence of cholangiocarcinoma in hamsters was chosen. Control hamsters and hamsters receiving 50 O viverrini metacercariae 40 days previously were each given 1.6 mg DMN orally. Mortality was significantly higher in the group receiving both DMN and parasites. Intrahepatic cholangiocarcinomas were found only in animals receiving both parasites and DMN. All tumors were mucin secreting and goblet cell metaplasia was a common feature. Tumors with an acinar type pattern contained an abundant connective tissue stroma and parasite egg granulomas were occasionally found in this stroma. Cholangiofibrosis and cystic cholangiomas were common in both groups, though cholangiofibrosis was more extensive in the group receiving both parasites and DMN. Cholangiocarcinomas appeared to arise either from hyperplastic processes in the bile duct wall or from areas of cholangiofibrosis distinct from major bile ducts. In both cases a range of transitional stages between hyperplasia and carcinoma were seen. Cholangiocarcinoma and cystic cholangioma were frequently seen in close proximity and appeared to have their origin in adjacent areas of cholangiofibrosis. (3 Refs)

18. CANCER INDUCTION AFTER PYLOROPLASTY IN RATS. TREATMENT WITH N-METHYL-N'-NITRO-N-NITROSOGUANIDINE.

Salmon RJ, Deschner EE, Okamura T, DeCosse JJ, Sherlock P (c/o Deschner), Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Arch Surg; 117(6):768-771 1982

Nineteen male Wistar rats received N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in drinking water (83 mg/L) to initiate glandular adenocarcinoma of the stomach; 8 control rats received tap water. After 12 wk a pyloroplasty was performed on nine rats receiving MNNG and three control rats. Ten MNNG-treated rats and 5 control rats had no operation. All were observed for 38 wk before being killed. No difference in the incidence of antral adenocarcinomas was found between the MNNG-treated groups; however, those without operation showed in situ changes in the duodenum and those treated with pyloroplasty showed five invasive adenocarcinomas. In this model pyloroplasty alone did not increase the risk of gastric cancer but increased the risk of duodenal tumors. Pyloroplasty apparently accelerated the gastric evacuation rate, resulting in greater insult to the duodenal mucosa. Such a condition may require a higher proliferative rate in the duodenum and may increase subsequent formation of malignant tumors. (Author abstract) (16 Refs)

19. DNA-METHYLATION BY NITROSOCIMETIDINE AND N-METHYL-N'-NITRO-N-NITROSOGUANIDINE IN THE INTACT RAT.

Gombar CT, Magee PN
Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Chem Biol Interact; 40(2):149-157 1982

The ability of the nitroso derivative of the drug cimetidine to interact with cellular macromolecules in the intact rat was investigated. Radio-labeled nitrosocimetidine was shown to methylate DNA in a variety of tissues in the rat after oral administration. Radioactivity was also detected in the RNA and protein extracted from these same tissues. Methylation of DNA by the parent compound, cimetidine, was not detected in any of the tissues studied. For comparison, the DNA methylation produced by the carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) dosed orally was measured. DNA alkylation by MNNG was found to be approx 2-36x greater than that produced by NC, varying with the tissues studied. The highest yield of DNA alkylation was found in the stomach for MNNG and the small intestine for nitrosocimetidine suggesting pharmacokinetic differences. (Author abstract) (23 Refs)

20. ILEOCECAL (PARACECAL) MALIGNANT LYMPHOMA--IMMUNOBLASTOMA--IN HOODED RATS.

Nemeth P, Schneider J, Warzok R
Korbontani Intezet, POTE, Szigeti u. 12, 7643 Pecs, Hungary
Morphol Igazsagugyi Orv Sz; 22(2):117-123 1982

Spontaneous and chemically induced ileocecal (paracecal) malignant lymphoma (immunoblastoma) was studied in inbred strain E hooded rats compared with untreated outbred Wistar rats. The spontaneous incidence of ileocecal immunoblastoma

was found to be 5% in 95 untreated hooded rats, and the tumors were detected between days 545 and 740 of life. The spontaneous incidence was found to be 0% among more than 400 untreated Wistar rats of two different strains. The immunoblastoma incidence was found to be 8-41% among hooded rats treated prenatally or postnatally with the combinations of ethylurea (0.5%), methylurea (0.2-0.3%), isopropylurea (0.4%), n-propylurea (0.4%), butylurea (0.4%) in drinking water or ephedrine (0.5% in feed) or Obesin (40 mg/kg) with sodium nitrite (0.2-0.5% in feed or 40 mg/kg 12 times every 2 wk through gastric probe). The incidence was found to be highest in the group treated with the combination of 0.4% propylurea and 0.3% sodium nitrite postnatally and lowest in that treated with 0.4% isopropylurea and 0.3% sodium nitrite postnatally. The tumors were detected in the treated animals between days 194 and 789 of life. The induced tumors were identified histologically as transfollicular immunoblastomas, showing no difference from the spontaneous ones. The tumor incidence was increased and the latent period shortened by treatment with the N-nitroso compounds. (22 Refs) (In HUN)

21. PRODUCTION OF KIDNEY TUMORS IN RATS WITH LOW DOSE OF DIMETHYLNITROSAMINE AFTER PARTIAL HEPATECTOMY.

Evarts RP, Brown CA, Mostafa MH
Lab. Carcinogen Metabolism, Div. Cancer Cause and Prevention, NCI, NIH, Public Health Service, U.S. Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 68(2):293-298 1982

The occurrence of kidney tumors in inbred Wistar rats as a result of dimethylnitrosamine (DMN) administration at different intervals after partial hepatectomy was studied. The schedule for DMN administration was determined on the basis of the levels of liver dimethylnitrosamine demethylase (DMN-d) at different intervals after the operation. DMN-d was 62% of the control values at 24 hr, 72% at 72 hr, and 96% at 92 hr after the operation. At these intervals a single dose of DMN (10 mg/kg body wt) was given to partially hepatectomized animals and to untreated controls. At termination, when the animals were 94 wk old, no kidney tumors were found in the control animals, whereas 23 of 54 animals (43%) that had been given injections of DMN 24 hr after partial hepatectomy developed kidney tumors. Kidney tumor incidence was 28 or 12%, respectively, when the carcinogen was administered 72 hr or 92 hr after the operation. The kidney tumor incidence and the activity of liver DMN-d were inversely related. (Author abstract) (27 Refs)

22. BACKSCATTERED ELECTRON IMAGING BY SEM OF NORMAL AND NEOPLASTIC URINARY BLADDER (MEETING ABSTRACT)

Smith GP, Williams AE
Teaching and Research Centre, University of Edinburgh, Western General Hospital, Edinburgh, Scotland
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

The study of urinary bladder cancer by scanning electron microscopy (SEM) has concentrated on the changes in luminal surface structure and organization during neoplasia. However, SEM backscattered electron imaging (BSE) of tissues stained with heavy elements such as silver allows visualization of subsurface structures. This method was used to examine normal and carcinogen treated rat bladders, and biopsies from patients under investigation for bladder cancer. Results show a predominance of binucleate superficial cells in the bladders of normal rats, and an organizational relationship between the superficial layer of cells and the underlying intermediary cell nuclei suggestive of the proliferative unit organization seen in epidermis. In rat bladders treated with methylnitrosourea, changes were observed in intracellular organization before urothelial changes could be observed histologically and by SEM examination of surface topology; superficial cells became predominantly uninuclear and the relationship between superficial and intermediary cells was lost. Areas where these changes have occurred can be readily observed at low magnifications. Preliminary observations of human biopsy material suggest that similar organizational and neoplastic changes occur. (3 Refs)

23. EXPERIMENTAL STUDY OF FUNCTIONAL STATE AND ENZYMATIC STRUCTURE OF PULMONARY ALVEOLAR MACROPHAGES AFTER PERORAL EXPOSURE TO DIMETHYLNITROSAMINE.

Merkur'eva RV, Litvinov NN, Aulika BV, Mukhambetova LKh, Bushinskaia LI, Dolinskaia SI, Iakimova ER, Konstantinova IN, Votiakov AV
Lab. Biochemistry, A. N. Sysin Inst. General and Community Public Health, Moscow, USSR
Biull Eksp Biol Med; 93(4):41-43 1982

Effect of peroral exposure to dimethylnitrosamine (DMNA: 30 mg/kg) on pulmonary alveolar macrophages was studied in male random-bred albino rats. DMNA administration produced progressive decrease of the number of viable alveolar macrophages. The decrease of macrophage count was associated with the increase of activities of microsomal acetylesterase and lysosomal beta-glucuronidase and the decrease of activity of mitochondrial malate dehydrogenase. (8 Refs) (In RUS)

24. INDUCTION OF SPERMIDINE N(1)-ACETYLTRANSFERASE BY DIALKYLNITROSAMINES.

Matsui I, Pegg AE
Dept. Physiology and Specialized Cancer Res. Center, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Cancer Res; 42(8):2990-2995 1982

Treatment of rats with dimethylnitrosamine (30 mg/kg) or diethylnitrosamine (200 mg/kg) produced a rapid increase in the activity of spermidine N1-acetyltransferase which peaked at values seven-fold greater than did control at 48 hr after exposure. This increase led to a small accumulation of N1-acetylspermidine in the liver but produced a more striking effect on putrescine which increased 30-to 40-fold after 2 days. Most of this increase appeared to be due to the conversion of N1-acetylspermidine into putrescine which is catalyzed by polyamine oxidase. Treatment with the nitrosamines also increased the conversion of spermine into spermidine which replaced the spermidine converted into putrescine. Spermine levels were therefore significantly depressed by treatment with these carcinogens. These results indicate that these hepatocarcinogens bring about an increase in putrescine and in the spermidine/spermine ratio in the liver not only by enhancement of ornithine decarboxylase but also by induction of the spermidine N1-acetyltransferase activity which is the rate-limiting step in the acetylase-oxidase pathway for interconversion of the polyamines. (Author abstract) (35 Refs)

MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS

25. INFLUENCE OF DELAYED ADMINISTRATION OF RETINYL ACETATE ON MAMMARY CARCINOGENESIS.

McCormick DL, Moon RC
Lab. Pathophysiology, Life Sciences Div., IIT Res. Inst., Chicago, IL, 60616
Cancer Res; 42(7):2639-2643 1982

Administration of a dietary retinoid supplement beginning 1 wk after carcinogen administration is highly effective in the inhibition of rat mammary carcinogenesis. A study was designed at two carcinogen dose levels to determine to what extent retinoid feeding can be delayed and retain its chemoprotective effect. In the high-dose experiments, groups of 30 virgin female Sprague-Dawley rats received a single iv dose of 50 mg N-methyl-N-nitrosourea (MNU) per kg body wt and were fed a dietary supplement of 328 mg retinyl acetate per kg diet beginning at 1, 4, or 8 wk after MNU administration. In the low-dose experiment, groups of 50 rats received 25 mg MNU per kg, and the retinoid was begun at 1, 4, 8, 12, 16, or 20 wk post-MNU. Controls at both dose levels received a placebo diet beginning 1 wk after carcinogen treatment. At the high MNU dose, retinyl acetate was most effective in inhibition of carcinogenesis when treatment was begun 1 wk after MNU administration. Delaying retinyl acetate feeding until 4 wk post-MNU resulted in slightly reduced chemoprotective efficacy, while an 8-wk delay caused a complete loss of anticancer activity. At the low MNU dose, delaying retinyl acetate administration for up to 12 wk after MNU administration caused no loss of chemopreventive efficacy. A 16-wk delay resulted in decreased anticancer activity, while retinoid treatment begun 20 wk post-MNU had no effect on cancer induction. Retinoid administration can be delayed beyond 1 wk and retain its activity against rat mammary carcinogenesis; the length of delay allowable without loss of activity is a function of tumor latency. (Author abstract) (15 Refs)

26. EFFECTS OF AROMATASE INHIBITOR 4-HYDROXYANDROSTENEDIONE AND OTHER COMPOUNDS IN THE 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED BREAST CARCINOMA MODEL.

Brodie AM, Garrett WM, Hendrickson JR, Tsai-Morris CH
Dept. Pharmacology and Experimental Therapeutics, Univ. Maryland Sch. Medicine, Baltimore, MD, 21201
Cancer Res; 42(8,Suppl):3360s-3364s 1982

Aromatase inhibitor, 4-hydroxyandrostene-3,17-dione (4-OHA), is a highly effective treatment in rats with 7,12-dimethylbenz(a)anthracene-induced hormone-dependent mammary tumors. Over 90% of tumors regress to less than one-half of their original size, and a high proportion regress completely. Treatment of rats with other inhibitors, 4-acetoxyandrostene-3,17-dione and 1,4,6-androstatriene-3,17-dione produce similar results. In comparison with other aromatase inhibitors, the compounds reduced ovarian estrogen secretion in the rat to the same extent as aminoglutethimide, whereas Teslac was without effect. The latter two compounds caused little and no regression of DMBA-induced mammary tumors, respectively. Our recent studies with 4-OHA, 4-acetoxyandrostene-3,17-dione, and 1,4,6-androstatriene-3,17-dione indicate that they interact with aromatase by a two-component mechanism, a rapid competitive inhibition, and a slower enzyme inactivation. Treatment of rats with 4-OHA also caused greater than 80% loss of ovarian aromatase activity in vivo and a reduction in ovarian estrogen secretion, which are maintained for at least 48 hr after injection. Although 4-OHA is cleared rapidly in vivo, the above results suggest that the compound has a sustained effect. Thus, when 7,12-dimethylbenz(a)anthracene-induced tumor-bearing rats were treated with 4-OHA injections on alternate wk, tumor regression continued to occur during wk without treatment. The overall regression was similar to that with continuous treatment. 4-OHA is also effective and similar to ovariectomy in rats with hormone-dependent metastatic mammary tumors produced by nitrosomethylurea. Our results indicate that mammary tumor regression induced by 4-OHA is mainly the result of the inhibition of aromatization, although other activities of the compound may also contribute. (Author abstract) (23 Refs)

27. EFFECT OF HIGH-DOSE OESTROGEN ADMINISTRATION ON THE GROWTH AND PROLACTIN RECEPTOR CONTENT OF N-NITROSOMETHYLUREA-INDUCED MAMMARY TUMOURS IN THE RAT.

Manni A, Rainieri J, Arafah BM, Pearson OH
Dept. Medicine, Case Western Reserve Univ., 2065 Adelbert Road, Cleveland, OH, 44106
J Endocrinol; 93(1):11-16 1982

The effect of chronic administration of a high dose of estradiol benzoate (OB) on growth and prolactin receptor content of the N-nitrosomethylurea (NMU)-induced rat mammary tumor was investigated. Daily im administration of 50 ug OB for 8 days to tumor-bearing rats induced marked reduction in tumor size which was already significant after only three injections. Simultaneous daily administration of 1 mg perphenazine to stimulate endogenous prolactin release counteracted the inhibitory effect on tumor growth of OB but only partially since the tumors grew significantly more when perphenazine was injected alone. No treatment significantly affected prolactin receptor content in the tumors. We concluded that administration of pharmacological doses of OB has a potent antitumor action on the NMU-induced rat mammary tumor. This effect can only partially be explained by inhibition of the peripheral action of prolactin. (Author abstract) (22 Refs)

28. STUDIES ON THE DETECTION AND CHARACTERIZATION OF INAPPARENT TRANSFORMED CELLS INDUCED BY NITROSOMETHYLUREA (NMU) IN MAMMARY GLANDS OF NEONATAL BALB/C MICE.

Lum KL
University of California, Berkeley, CA
Diss Abstr Int [B]; 42(12,pt1):4750-B 1982

Neonatal BALB/c female mice were treated beginning at one day of age with 100 ug or 300 ug NMU. Some mice from each of the NMU dosage groups were simultaneously given daily subcutaneous injections of 100 ug deoxycorticosterone (DCA), 0.2 ug estradiol-17beta, 250 ug ovine prolactin (NIH-PS-11) whereas the rest were given only vehicle. All animals were sacrificed at 6-8 days of age and their number 2 mammary glands transplanted as pieces into the gland-free fat pads of 3 week isogeneic virgin mice. Randomly selected glands from all transplant groups were wholemounted after 17 weeks of growth and shown to contain only normal outgrowths. The remaining outgrowths were enzymatically dissociated into single cell suspensions which were then injected into the gland-free fat pads of 3 week BALB/c assay hosts at 10(5) cells per fat pad. These injected cell suspensions gave rise to both normal outgrowths and a variety of morphologically distinct abnormal

outgrowths. The incidence of these abnormal outgrowths in the assay glands was dependent upon the dose of NMU used to treat the original neonatal donor mice and on the presence or absence of simultaneous mammotropic hormone treatment. Outgrowths derived from mice given 100 ug NMU without hormone treatment produced an 8% incidence of abnormal outgrowths in the assay glands. Those from mice treated with 100 ug NMU with hormone treatment had a 14% incidence whereas the group treated with 300 ug NMU without hormones had an incidence of 44%. Finally, the group treated with 300 ug NMU and hormones had an incidence of 92%. (no Refs)

29. EFFECTS OF DIETARY LIPIDS ON LACTOGENIC HORMONE RECEPTOR BINDING IN RAT MAMMARY TUMORS.

Cave WT, Erickson-Lucas MJ
Endocrine Unit, Dept. Internal Medicine, Univ. Rochester Sch. Medicine, St. Mary's Hosp., 89 Genesee St., Rochester, NY, 14611
JNCI; 68(2):319-324 1982

Both epidemiologic studies in humans and experiments in laboratory animals have indicated that high-fat (HF) diets promote mammary tumor growth; however, the biochemical mechanisms responsible for this accelerated tumor growth are poorly understood; thus this study was designed to determine whether diet-induced alterations in the lipid composition of mammary tumor cell membranes were associated with differences in lactogenic hormone binding capacity. Mammary tumors were induced with N-methyl-N-nitrosourea in 50-day-old female inbred Buffalo rats that were maintained on either HF or low-fat (LF) diets composed of either 20% corn oil or 0.5% corn oil, respectively. The microsome-membrane fractions of these tumors were then analyzed for specific lactogenic hormone binding with the use of 125I-labeled human growth hormone. Methylated extracts of these same membrane fractions were also subjected to gas-liquid chromatography. Our results demonstrated that the mammary tumor membranes of the HF group did have a significantly greater lactogenic binding capacity than those of the LF group and that these differences in hormone binding were accompanied by significant alterations in the membrane qualitative fatty acid profiles of each group. Therefore, one way in which dietary lipids may be able to influence mammary tumor growth is by modification of the lactogenic hormone binding capacity of tumor cell membranes. (Author abstract) (27 Refs)

30. INFLUENCE OF ORAL SUPPLEMENTATION OF ASCORBATE UPON THE INDUCTION OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE.

Kawasaki H, Morishige F, Tanaka H, Kimoto E
(c/o Kimoto) Dept. Chemistry, Faculty Science, Fukuoka Univ., 11 Nanakuma, Nishi-ku, Fukuoka 814, Japan
Cancer Lett; 16(1):57-63 1982

The influence of oral supplementation of ascorbic acid (AA) upon the induction of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) gastric cancer was investigated in young male Wistar rats. When MNNG-initiated rats (167 ug/ml in the drinking water) were fed a diet containing a daily dose of 0.4 g sodium ascorbate (AA), no significant tumor inhibition was observed, although AA supplementation reduced the grade of the lesion to some extent. When AA supplementation was not begun until 210 days after MNNG, at a time when adenomatous hyperplasia of the stomach epithelium was evident, again, no significant tumor inhibition was observed. AA supplementation in these animals did result in a significant reduction in the grade of the gastric lesions produced, however. Though adenocarcinoma cells seemed to be induced in AA supplemented animals, their downward massive growth, as occurred in animals not supplemented with AA, was inhibited by a heavy proliferation of connective tissue fibers surrounding them. Tumor masses were thus effectively encapsulated by connective tissue in AA supplemented animals. (14 Refs)

31. EFFECT OF HEMITHYROIDECTOMY AND 3-AMINO-1,2,4-TRIAZOLE ON THYROID TUMORS INDUCED BY N-BIS(2-HYDROXYPROPYL)-NITROSAMINE IN RATS.

Iwata C
First Dept. Pathology, Nara Medical Univ., Nara, Japan
Nara Igaku Zasshi; 32(6):670-684 1981

Thyroid tumors were induced in male Wistar rats administered 70 mg/100 g body wt of N-bis(2-hydroxypropyl)nitrosamine (DHPN), and the effects of 3-amino-1,2,4-triazole (amitrole) on the tumors were studied. Rats were given the DHPN 1x/wk for 4, 8, 12, 16, and 20 wk with or without undergoing hemithyroidectomy at day 10. Thyroid tumors developed in 10/20 rats given DHPN alone. Thyroid tumors also occurred in rats given DHPN and hemithyroidectomy. Amitrole (2,000 ppm, po) was administered to 11 rats for 12 wk following treatment with DHPN (1x/wk x 4), and the following 4 wk the rats were given a stock diet. Thyroid tumors developed in 10/11 rats. Results indicated that amitrole did not induce thyroid tumors when given alone, but amitrole and hemithyroidectomy, in combination with DHPN, increased the development of thyroid tumors compared to administration of DHPN alone. (37 Refs) (In JPN)

32. PITUITARY RESPONSES TO THYROTROPIN-RELEASING HORMONE AFTER TREATMENT WITH THE BREAST CARCINOGEN NITROSOMETHYLUREA: INHIBITION OF PROLACTIN BUT NOT THYROTROPIN RELEASE.

Kieffer JD, Maloof F, Vickery AL, Mover H, Downing M, Ridgway EC
Thyroid Unit, Massachusetts General Hosp., Boston, MA, 02114
Endocrinology; 110(6):1892-1896 1982

N-Nitrosomethylurea (NMU) is a widely used experimental breast carcinogen. The present report describes the effects of NMU on the plasma PRL and TSH increases in response to exogenous TRH. Female Buffalo rats, 75-80 days old, were given a single ip injection of NMU (10 mg/100 g) or vehicle. At various times after injection, NMU-treated rats and vehicle-injected controls were tested with exogenous TRH (625 ng/100 g, ip). Groups of four to six rats were bled at 10, 20, 30, 45, and 60 min after TRH and at 10 min after saline (baseline group). The response to TRH (delta) was determined by subtracting the mean plasma PRL or TSH level of the baseline group from the mean peak level observed after TRH. For four separate control experiments, deltaPRL averaged 104 +-19 ng/ml (mean +- SE). At 20 hr, 42 hr, 6 days, and 2, 3, 4, 8, and 12 wk after NMU, deltaPRL was 87, 0, 0, 16, 10, 3, 49, and 65 ng/ml, respectively. deltaPRL was statistically significant in all four control experiments, and remained significant at 20 hr after NMU. However, from 42 hr through 4 wk, no significant deltaPRL occurred. A significant deltaPRL reappeared at 8 and 12 wk, the approximate time of appearance of the first palpable breast cancers. Pituitary PRL concentrations (micrograms PRL per mg protein) were significantly lower in NMU-treated groups than in vehicle-treated controls at 42 hr, 3 wk, and 12 wk. In contrast to its marked inhibitory effect on

deltaPRL, NMU had no effect on deltaTSH. This is consistent with the hypothesis that treatment with NMU resulted in a selective impairment of pituitary PRL-secreting cells. Moreover, our data show that the plasma PRL response to TRH was inhibited at times after NMU when pituitary PRL was not significantly depleted. This observation is in accord with the concept of impairment of either TRH receptor binding or events which couple receptor binding and hormone release. (Author abstract) (38 Refs)

MUTAGENICITY OF NITROSO COMPOUNDS

33. MUTAGENICITY OF N-NITROSO BILE ACID CONJUGATES IN SALMONELLA TYPHIMURIUM AND DIPLOID HUMAN LYMPHOBLASTS.

Puju S, Shuker DE, Bishop WW, Falchuk KR, Tannenbaum SR, Thilly WG

(c/o Tannenbaum) Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139

Cancer Res; 42(7):2601-2604 1982

Two N-nitroso bile acid conjugates, N-nitrosotaurocholic acid and N-nitrosoglycocholic acid, were tested for mutagenicity by forward mutation assay in Salmonella typhimurium TM 677 and in diploid human lymphoblasts, line TK6. N-Nitrosoglycocholic acid and N-nitrosotaurocholic acid showed similar concentration-response curves in the bacterial assay with statistically significant mutant fractions observed at about 0.12 mM. Non-nitrosated parent compounds were nonmutagenic. However, in the human cell assay, N-nitrosotaurocholic acid gave statistically significant mutant fractions only at 0.4 mM, but N-nitrosoglycocholic acid was mutagenic at 0.05 uM, some 9,000x more potent. Experiments with quantitative Ames' S typhimurium reversion assays indicated mutagenesis via base substitution. (Author abstract) (11 Refs)

34. DOSE-RESPONSE CURVE FOR ETHYLNITROSOUREA-INDUCED SPECIFIC-LOCUS MUTATIONS IN MOUSE SPERMATOGONIA.

Russell WL, Hunsicker PR, Raymer GD, Steele MH, Stelzner KF, Thompson HM

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Proc Natl Acad Sci USA; 79(11):3589-3591 1982

The extreme mutagenic effectiveness of N-ethyl-N-nitrosourea in the mouse has permitted the accumulation of the most extensive dose-response data yet obtained for chemical induction of specific-locus mutations in spermatogonia. In the lower portion of the curve, below a dose of 100 mg/kg, the data fall statistically significantly below a maximum likelihood fit to a straight line. Independent evidence indicates that, over this dose range, ethylnitrosourea reaches the testis in amounts directly proportional to the injected dose. It is concluded that, despite the mutagenic effectiveness of ethylnitrosourea, the spermatogonia are apparently capable of repairing at least a major part of the mutational damage when the repair process is not swamped by a high dose. This finding is important both in basic studies on the mutagenic action of chemicals in mammals and in risk estimation. (Author abstract) (15 Refs)

35. EFFECT OF DOSE FRACTIONATION ON THE ETHYLNITROSOUREA INDUCTION OF SPECIFIC-LOCUS MUTATIONS IN MOUSE SPERMATOGONIA.

Russell WL, Hunsicker PR, Carpenter DA, Cornett CV, Guinn GM

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Proc Natl Acad Sci USA; 79(11):3592-3593 1982

As measured by specific-locus mutations in mouse spermatogonia, fractionating a dose of 100 mg of ethylnitrosourea per kg of body weight into doses of 10 mg/kg injected intraperitoneally at weekly intervals greatly reduces the mutation frequency compared with that from a single dose of 100 mg/kg. Because there is independent evidence that the doses of 10 and 100 mg/kg reach the germ cells in amounts directly proportional to the injected dose, the lower mutational response with the fractionated dose is attributed to repair. The induced mutation rate expected from a single 10-mg/kg dose (on the assumption that this would be 1/10th the rate observed after 10 such doses) would be only 75% of the spontaneous mutation rate. Mouse spermatogonia apparently have an efficient repair system that is effective even against a potent mutagen. (Author abstract) (5 Refs)

36. COMPARISON OF MICROSOMAL INDUCER PRETREATMENT ON THE IN VITRO ALPHAHYDROXYLATION AND MUTAGENICITY OF N-NITROSOPYRROLIDINE IN RAT AND HAMSTER LIVER.

McCoy GD, Hecht SS, McCoy EC

Dept. Epidemiology and Community Health, Inst. for the Environmental Health Sciences, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH, 44106

Environ Mutagen; 4(3):221-230 1982

Reasonable agreement is demonstrated between rates of microsomal alpha-hydroxylation of N-nitrosopyrrolidine (NPYR) and the metabolic activation of NPYR to a mutagen by post-mitochondrial supernatants when changes in microsomal protein are taken into account. The Ames assay for mutagenicity was employed with use of Salmonella typhimurium strain TA 1535. Rats and hamsters were pretreated with 3-methylcholanthrene (MC), phenobarbital (PB) or Aroclor 1254 (AR). In the rat, most active post-mitochondrial supernatant preparations were obtained with PB and AR while in hamsters AR was most effective in increasing mutagenicity of NPYR. The influence of the various modifiers of mixed function oxidase activity on protein content was determined on liver subfractions. In the rat, no difference was observed in the protein content of post-mitochondrial or post-microsomal supernatant while all the inducers increased these parameters in the hamster. The same pretreatments were tested on the rate of microsomal alpha-hydroxylation of NPYR. In the rat, only AR pretreatment resulted in significant enhancement, while MC slightly decreased the rate. In the hamster, both MC and AR pretreatment markedly increased the rate. When NPYR alpha-hydroxylase is expressed per g of wet wt of liver, differences in the amount of microsomal protein are included and better agreement between metabolism and mutagenicity in PB pretreated animals is obtained. MC and AR pretreatment increased aldehyde dehydrogenase activity in post microsomal supernatants in both rats and hamsters, while PB only increased the activity in hamster preparations. (26 Refs)

37. SPECIES-SPECIFIC ACTIVATION OF PHENACETIN INTO BACTERIAL MUTAGENS BY HAMSTER LIVER ENZYMES AND IDENTIFICATION OF N-HYDROXYPHENACETIN O-GLUCURONIDE AS A PROMUTAGEN IN THE URINE.

Camus AM, Friesen M, Croisy A, Bartsch H
(c/o Bartsch) Programme Environmental Carcinogens and Host Factors, International Agency Res. on Cancer, 150 cours Albert-Thomas, 69372 Lyon Cedex 08, France
Cancer Res; 42(8):3201-3208 1982

Phenacetin was mutagenic in Salmonella typhimurium TA100 in plate assays when liver fractions from Aroclor-treated hamsters, but not rats, were used. Its known or putative metabolites were synthesized; of these, N-hydroxyphenacetin and N-acetoxyphenacetin were found to be mutagenic in liquid and plate assays, both requiring activation by liver fractions from Aroclor-treated hamsters. 2-Hydroxyphenacetin and 2-acetoxyphenacetin were nonmutagenic. N-Hydroxyphenetidine (the deacetylated metabolite of phenacetin) and p-nitrosophenetole were the only products that were found to be mutagenic per se when assayed under N2 in either Salmonella TA100 and TA100 NR (nitroreductase-deficient) strains. Phenacetin was administered to male BDVI rats and Syrian golden hamsters, and its urinary metabolites were deconjugated with beta-glucuronidase:arylsulfatase. After reactivation by hamster liver fractions, mutagenicity was demonstrated in S typhimurium TA100 with urine from phenacetin-treated hamsters, but not with that from rats. After treatment with deconjugating enzymes, N-hydroxyphenacetin was isolated from hamster urine by high-performance liquid chromatography and identified by mass spectral analysis. The data support the conclusions that (a) N-hydroxyphenacetin is a proximate mutagenic metabolite of phenacetin which, after N-deacetylation, is responsible for the mutagenicity observed in vitro and in the urine of hamsters and (b) the higher yield of N-hydroxyphenacetin that is formed in the liver of hamsters as compared to rats explains the pronounced species-specific activation of phenacetin into bacterial mutagens. (Author abstract) (59 Refs)

38. METABOLIC ACTIVATION OF BENZO[A]PYRENE, AFLATOXIN B1, AND DIMETHYLNITROSAMINE BY A HUMAN HEPATOMA CELL LINE.

Huh N, Nemoto N, Utakoji T
Institut fur Zellbiologie (Tumorforschung),, Universitat Essen (GH), Hufelandstrasse 55, 4300 Essen 1, W. Germany
Mutat Res; 94(2):339-348 1982

The frequency of sister-chromatid exchanges (SCE) was measured in normal human fibroblasts (TIG-II) co-cultivated with human hepatoma huH-1 cells to assess the genotoxic effect of activated chemicals aflatoxin B1 (AFB), benzo[a]pyrene (B[a]P), N,N-dimethylnitrosamine (DMN), and 1,2-benzanthracene. When huH-1 cells were treated with 13 uM BA for 24 hr, aryl hydrocarbon hydroxylase activity was induced to 920 picomoles/mg protein/hr, which was approx 24x higher than the basal level. SCE frequency in TIG-II cells changed depending on the inoculum ratio of huH-1 cell to TIG-II cells in the co-culture containing 5 uM AFB. When the inoculum size of huH-1 cells was half that of TIG-II cells, the SCE frequency in TIG-II cells was markedly enhanced over the control level that remained in plateau even in the cultures with larger inocula of huH-1 cells. In the co-culture, the SCE frequency was increased depending on the dose of B(a)P: 0.1 and 12.5 uM of B(a)P induced 7.2 and 10.7 SCE/metaphase, respectively. In the cultures of TIG-II cells only, 0.5 uM of B(a)P showed no significant increase of SCE, while 2.5 and 12.5 uM of B(a)P slightly elevated the SCE frequency over the control level. Treatment with DMN increased the incidence of SCE far more efficiently in the co-cultivation than in cultures of TIG-II cells only. The SCE frequency induced by 0.4 milliM (mM) of DMN in the cultures with huH-1 cells was comparable with that induced by 10 mM of DMN without huH-1 cells. (41 Refs)

39. MOUSE SPOT TEST WITH ALKYLNITROSOUREAS.

Shibuya T, Murota T, Tutikawa K
Lab. Genetics, Hatano Res. Inst., Food and Drug Safety Center, 729-5 Ochiai, Hadano, Kanagawa-ken 257, Japan
Mutat Res; 104(4/5):311-315 1982

Mutagenicity tests for various alkylnitrosoureas such as N-methyl-N-nitrosourea (MNU), N-ethyl-N-nitrosourea (ENU), N-propyl-N-nitrosourea (PNU), and N-butyl-N-nitrosourea (BNU) were carried out using the mouse spot test and both color spots and development of tests were observed. MNU, which had the most teratogenic effect, produced hydrocephalus in F1 offspring. All of the offspring died within 2 or 3 days after birth at doses greater than 6.25 mg/kg. Mice given 3.125 mg/kg showed the possible induction of color spots. ENU induced color spots in offspring. Color spots were observed in approx 20% of mice injected with 50 mg/kg ENU, and the incidence increased dose-dependently. Dose-dependency was also observed in PNU-treated mice, but the incidence of color spots was lower than that in the ENU group. In the BNU group, the incidence of color spots was approx 10% when the mice had been injected with 100 mg/kg BNU. The wt of the testes in the treated groups was significantly less than that in the control group. The decrease was especially significant in the ENU-treated group. In the BNU-treated group, the decrease was less marked than in the ENU- and PNU-treated groups. Retardation in the development of the testis was observed histologically in the alkylnitrosourea-treated F1 30-day-old males. Fertility of males in all treated groups, however, was normal when examined 60 days after birth. (14 Refs)

40. GENETIC ANALYSIS OF AN N-ETHYL-N-NITROSOUREA-INDUCED MUTATION AT THE HEMOGLOBIN BETA-CHAIN LOCUS IN MICE.

Murota T, Shibuya T, Tutikawa K
Lab. Genetics, Hatano Res. Inst., Food and Drug Safety Center, 729-5 Ochiai, Hadano, Kanagawa-Ken 257, Japan
Mutat Res; 104(4/5):317-321 1982

Mutagenicity of N-ethyl-N-nitrosourea (ENU) at a hemoglobin beta-chain (Hbb) locus and at visible loci in spermatogonia of mice was studied. Preliminary results of specific-locus tests with ENU in mice and of genetic analysis on an ENU-induced Hbb locus mutation are reported. One mutant at the Hbb locus and nine mutants at visible loci were obtained. Findings indicated that the mutant could have originated from the treated mice and that the mutation is heritable and viable under homozygous conditions; the mutation may originate from a gene mutation at the base-pair level. (12 Refs)

41. CELL KILLING BY VARIOUS NITROSOUREAS AND THE POTENTIATING EFFECT OF CAFFEINE.

Goth-Goldstein R
Lab. Radiobiology and Environmental Health, Univ. California, San Francisco, CA, 94143
Mutat Res; 94(2):237-244 1982

The extent of sensitization by caffeine of cell killing by carmustine (BNCU), lomustine (CCNU), chlorozotocin (CHLZ),

N-ethyl-N-nitrosourea (ENU), N-methyl-N-nitrosourea (MNU), and 1,3-bis(trans-4-hydroxycyclohexyl)-1-nitrosourea (BHCNU) was investigated in Chinese hamster bone marrow cells (650A cells). When killing of 650A cells by the various nitrosoureas was determined as a function of amount of drug decomposed in the exposure interval, the loss of colony-forming ability varied considerably with the nitrosourea used, although all agents gave a shouldered response. Cell killing by BCNU and CCNU was highest, followed by CHLZ then BHCNU; ENU was much less toxic than any of the other agents. The mean lethal dose (D0) values for BCNU, CCNU, CHLZ, and BHCNU ranged between 1.8 and 6 uM, whereas that for ENU was 2,100 uM. For all drugs, the extrapolation number, n, was between 2-7 except for BHCNU, for which it was 29. Caffeine, at a nontoxic dose in untreated cells (1 milliM), reduced the survival of cells after treatment with ENU, BCNU, CCNU, or CHLZ. Caffeine reduced the shoulder and the D0, potentiating cell killing with ENU the most, with CHLZ the least. However, after treatment with BHCNU, the presence or absence of caffeine had no effect on the colony-forming ability of the cells. Results indicated that potentiation of cell killing by caffeine is based on the reaction of a drug with the cellular DNA. (31 Refs)

42. FORMATION OF THE CROSS-LINK 1-[N(3)-DEOXYCYTIDYL],2-[N(1)-DEOXYGUANOSINYL]ETHANE IN DNA TREATED WITH N,N'-BIS(2-CHLOROETHYL)-N-NITROSOUREA.

Tong WP, Kirk MC, Ludlum DB
(c/o Ludlum) Div. Oncology, Dept. Medicine, Albany Medial Coll., Albany, NY, 12208
Cancer Res; 42(8):3102-3105 1982

The cross-linked dinucleoside, 1-[N3-deoxycytidyl],2-[N1-deoxyguanosinyl]ethane, has been isolated from DNA which has been exposed to N,N'-bis(2-chloroethyl)-N-nitrosourea. It is probable that this structure is responsible for the interstrand cross-linking observed previously by physical methods. The modification is unique in that it cross-links DNA through two base-pairing positions and probably arises through the transfer of a chloroethyl group to one of the bases followed by a second reaction of this group with the other strand of DNA. Initial attack could be at the N3 position of deoxycytidine, the N1 position of deoxyguanosine, or possibly the O6 position of deoxyguanosine. Attack at the O6 position of deoxyguanosine would require an internal cyclization with the N1 position of deoxyguanosine before secondary reaction with the N3 position of deoxycytidine but would explain resistance to N,N'-bis(2-chloroethyl)-N-nitrosourea in cells capable of removing substituents on the O6 position of guanine. (Author abstract) (12 Refs)

43. ALKYLARYLNITROSOUREAS: STABILITY IN AQUEOUS SOLUTION, PARTITION COEFFICIENT, ALKYLATING ACTIVITY AND ITS RELATIONSHIP TO SCE INDUCTION IN CHINESE HAMSTER V79-E CELLS.

Mendel J, Thust R, Schwarz H
Res. Group for Preventive Oncology, Inst. Pathology of the Medical Acad. Erfurt, Nordhauser Strasse 74, DDR-5000 Erfurt, E. Germany
Arch Geschwulstforsch; 52(5):371-377 1982

The alkylating activity, chemical stability, and partition coefficient were determined for eight nitrosourea derivatives. Test compounds were compared with 1-methyl-1-nitrosourea and 1-ethyl-1-nitrosourea. Decomposition in aqueous soln was influenced by the 1-N and 3-N substituents. The alkylating activity of mono- and di-substituted nitrosoureas correlated roughly with induction of sister chromatid exchanges (SCE) in Chinese hamster V79-E cells. However, 1-methyl-3-naphthyl-1-nitrosocarbamate had low alkylating activity but high SCE-inducing activity. 1,3-Dimethyl-3-phenyl-1-nitrosourea had no detectable alkylating activity but was the strongest SCE inducer. (28 Refs)

44. MUTAGENIC RESPONSES OF FIVE INDEPENDENT GENETIC LOCI IN CHO CELLS TO A VARIETY OF MUTAGENS. DEVELOPMENT AND CHARACTERISTICS OF A MUTAGEN SCREENING SYSTEM BASED ON SELECTION FOR MULTIPLE DRUG-RESISTANT MARKERS.

Gupta RS, Singh B
Dept. Biochemistry, McMaster Univ., Hamilton L8N 3Z5, Canada
Mutat Res; 94(2):449-466 1982

Response of several well characterized genetic markers such as those involving resistance to thioguanine, emetine, ouabain, 5-6-dichlororibofuranosylbenzimidazole, and methylglyoxal bisguanylhydrazone towards a number of direct- and indirect-acting mutagens was assessed in proline-requiring Chinese hamster ovary (CHO) cell line. Direct-acting alkylating and DNA-adduct forming agents such as beta-propiolactone, ethyleneimine, N-nitrosomethylurea, 4-nitroquinoline-N-oxide, methyl methanesulfonate, and ethyl methanesulfonate; DNA intercalating and cross-linking agents such as ICR-170, acridine orange, ethidium bromide, mitomycin C, and actinomycin D; and chemicals requiring microsomal activation in other systems such as benzo[a]pyrene, 7,12-dimethylbenz[a]anthracene, benzidine, and beta-naphthylamine were examined. The response of various agents was determined at only two or three concentrations which should have resulted in between 10-80% cell killing. Mutation frequencies of different genetic markers which were observed in the control and mutagen-treated cultures, as well as the mutagenesis significance ratio of various markers, which provide a measure of their relative mutagenic response are shown. Of the genetic loci, no one single locus showed higher response to all of the chemicals, instead, depending upon the chemical, specific loci were found to be more responsive than others. Results indicated that CHO cells possess significant capacity for the metabolic activation of many procarcinogens, and also underscore the merits of measuring the mutagenic response at multiple genetic loci in mutagen screening studies. (40 Refs)

45. EFFECT OF PRAZIQUANTEL, A NEW ANTISCHISTOSOMAL DRUG, ON THE MUTATION AND TRANSFORMATION OF MAMMALIAN CELLS.

Billings PC, Heidelberger C
(c/o Heidelberger) Comprehensive Cancer Center Res. Lab., Univ. Southern California, Los Angeles, CA, 90033
Cancer Res; 42(7):2692-2696 1982

Praziquantel (PQ), a tetrahydroquinoline derivative, is a new clinically effective antischistosomal drug, which has been shown to lack or to possess very weak mutagenic activity. However, in bacteria, this compound can act as a weak comutagen that increases the mutagenicity of several chemical mutagens and carcinogens. We have found that PQ can act as a very weak comutagen in animal cells. At 10 to 50 ug/ml, PQ increased the mutagenicity of N-methyl-N'-nitro-N-nitrosoguanidine and 2-methoxy-6-chloro-9-[3-(2 chloroethyl)amincpropylamino]acridine dihydrochloride about two-fold in Chinese hamster V-79 cells. In C3H/10T1/2 mouse

embryo cells, PQ exhibited only negligible comutagenic activity. PQ did not oncogenically transform C3H/10T1/2 cells but had a pronounced effect on 3-methylcholanthrene-induced transformation of these cells. When PQ was coadministered with or added after 3-methylcholanthrene treatment, the number of Type III foci produced was about five-fold lower than in cultures treated with 3-methylcholanthrene alone. Therefore, PQ can inhibit Type III focus formation in C3H/10T1/2 cells. (Author abstract) (16 Refs)

46. IN VIVO SISTER CHROMATID EXCHANGE AND CELLULAR REPLICATION KINETICS OF NORMAL AND LYMPHOMA AKR BONE MARROW CELLS.

Biegel JA, Boggs SS, Conner MK
Univ. Pittsburgh Sch. Medicine, RC510 Scaife Hall, Pittsburgh, PA, 15261
Cancer Res; 42(7):2813-2815 1982

The recent development of an AKR(Rb6.15)1Ald lymphoma model in our laboratory presents a unique means of comparing sister chromatid exchange (SCE) frequencies and cellular replication kinetics of normal and lymphoma cells in the same host environment. Lymphoma cells, distinguished from normal cells by the presence of two metacentric chromosomes, had an average cell cycle time of 8 hr compared to 11 hr for normal cells. Normal bone marrow cells from nonleukemic AKR/J, nonleukemic AKR(Rb6.15)1A1d, and tumor passage recipients had similar base-line and 1,3-bis(2-chloroethyl)-1-nitrosourea-induced SCE frequencies following exposure to 4.4 mg 1,3-bis(2-chloroethyl)-1-nitrosourea per ml and 19 hr 5-bromo-2-deoxyuridine. While base-line SCE frequencies were only slightly higher, 1,3-bis(2-chloroethyl)-1-nitrosourea-induced lymphoma cell SCE frequencies were 3x higher than normal induced SCE frequencies [34.06 +-6.6 (SE) versus 11.0 +-0.6 SCEs/cell]. (Author abstract) (11 Refs)

47. CELLULAR REPLICATION KINETICS AND PERSISTENCE OF SISTER CHROMATID EXCHANGE-INDUCING LESIONS IN NORMAL AND LYMPHOMA AKR CELLS FOLLOWING EXPOSURE TO 1,3-BIS(2-CHLOROETHYL)-1-NITROSOUREA.

Biegel JA, Conner MK, Boggs SS
Univ. Pittsburgh Sch. Medicine, RC510 Scaife Hall, Pittsburgh, PA, 15261
Cancer Res; 42(7):2816-2820 1982

The present studies were designed to evaluate the role of cell cycle time and time of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) administration on the persistence of sister chromatid exchange (SCE)-inducing lesions in normal and lymphoma second- and third-division AKR bone marrow cells. Normal second-division cells harvested from mice given injections of BCNU at the start of an 18-, 24-, or 28-hr 5-bromo-2-deoxyuridine (BrdUrd) infusion exhibited similar linear dose-dependent increases in SCE frequencies. The faster-cycling lymphoma cells, harvested after 18-hr BrdUrd infusion, had significantly higher base-line and BCNU-induced increases in SCE frequencies than did normal cells. Dose-dependent increases in SCE frequencies were demonstrated in third-division normal and lymphoma cells from mice infused with BrdUrd for 24 or 28 hr. BCNU dose-dependent increases in SCE frequencies were also observed following injection of BCNU 8 hr after the start of BrdUrd infusion. The unexpectedly higher levels of SCEs for both normal and lymphoma cells by this treatment protocol may be due to SCEs occurring at the same site in successive divisions in BrdUrd. Lower nonreciprocal SCE frequencies were observed in third-division cells relative to SCE frequencies in second-division cells; a possible consequence of the cytotoxicity of BCNU. Injection of BCNU produced significant changes in the proportions of normal and lymphoma cells completing one, two, or three or more divisions in BrdUrd. Lymphoma cells were consistently more sensitive to the specific type(s) of BCNU-induced damage leading to SCEs and cell death than were normal cells. These studies indicated that differences in SCE response were not due to cell cycle time, time of drug administration, or potential for repair. It is therefore suggested that increased sensitivity of lymphoma vs normal cells may be due to increased cellular uptake of BCNU. (11 Refs)

48. SISTER CHROMATID EXCHANGE RESPONSE OF HUMAN DIPLOID FIBROBLASTS AND CHINESE HAMSTER OVARY CELLS TO DIMETHYLNITROSAMINE AND BENZO(A)PYRENE.

Tomkins DJ, Kwok SE, Douglas GR, Biggs D
Dept. Pediatrics, McMaster Univ. Health Sciences Centre, Hamilton, Ontario L8N 3Z5, Canada
Environ Mutagen; 4(3):203-214 1982

A study was undertaken to examine the possibility that Chinese hamster ovary (CHO) and human diploid fibroblasts may not show the same sensitivity to well known carcinogens benzo(a)pyrene (BP) and dimethylnitrosamine (DMN), using a metabolic activation system and sister chromatid exchange (SCE) analysis. Metabolic activation in the tests was accomplished with a microsomal fraction from rats induced with Aroclor 1254. The human diploid lines employed were IMR-90, WI-8, and S-3299. For both BP and DMN the human cells and CHO cells showed dose-response slopes that were significantly different from zero, except for CHO cells treated with BP for 1 hr and S-3299 cells treated with DMN. While the responses of the human and CHO cells to BP, and the responses of the human cells to BP and DMN were similar, the dose-response of the human cells to DMN was statistically less significant than that of CHO cells. Reducing the period of treatment of CHO cells from 1.0 hr to 0.5 hr had no effect on the slope of the dose-response curves for BP and DMN. The observed differences between human and CHO cells may reflect differences in the fate of metabolic intermediates of DMN. (38 Refs)

49. KINETICS OF INDUCTION OF SISTER-CHROMATID EXCHANGES BY X-RAYS THROUGH TWO CELL CYCLES.

Renault G, Gentil A, Chouroulinkov I
Institut de Recherches Scientifiques sur le Cancer, B.P. No. 8, 94802 Villejiuf Cedex, France
Mutat Res; 94(2):359-368 1982

Sister chromatid exchange (SCE) induction by x-rays delivered at various times during the two cell cycles needed to obtain harlequin-stained chromosomes (metaphases II) was studied in V79 Chinese hamster cells that were allowed to incorporate 5-bromo-2'-deoxyuridine (BrdUrd) for only 6 hr during the first cell cycle. A linear dose-response was obtained when the x-irradiation was performed just prior to the BrdUrd addition. When the x-irradiation was performed during the first cell cycle, the number of SCE progressively increased, and then reached a plateau during the BrdUrd incorporation. The kinetics of SCE induction with N-methyl-N'-nitro-N-nitrosoguanidine was different: no increase was observed during the first cell cycle, and the SCE frequency significantly decreased with the completion of the S phase of both the first and the second cell cycles. After the addition of BrdUrd, the G1 phase

appeared first and the G2 phase appeared at the end. The cell cycle was longer for the x-irradiated cells than that for the unirradiated controls, and at the ordinate of 50% tritium-labeled metaphases II, the S-phase duration was 7.5 hr for the former and 6.5 hr for the latter. While the number of dicentric chromosomes decreased when cells passed from G1 to S, the frequency of chromosomal aberrations remained stable until the late S phase and a small decrease was observed in G2. The chromatid-type aberration frequency was enhanced by a factor of 3 between G1 and early-middle S. Approx 25% of the cells showed no aberration when x-irradiation was performed prior to the S phase. (16 Refs)

50. NEUROBLAST OF THE GRASSHOPPER EMBRYO AS A NEW MUTAGEN TEST SYSTEM. II. CHROMOSOME BREAKAGE INDUCED BY IN VITRO EXPOSURE OF EMBRYOS TO THE DIRECT-ACTING MUTAGENS 4NQO, MMNG, ADRIAMYCIN, AND BLEOMYCIN.

Liang JC, Gaulden ME
(c/o Gaulden) Radiation Biology Section, Dept. Biology, Univ. Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, TX, 75235
Environ Mutagen; 4(3):279-290 1982

Embryos of the grasshopper Chortophaga viridifasciata (De Geer) were used in a new mutagen test system at a stage equivalent to 14-day development at room temperature. Embryos were separated from yolk and put in 35 mm x 10 mm plastic petri dishes which contained 5 ml of Mark's M-20 culture medium with 7.5% fetal calf serum plus antibiotics. Adriamycin (ADM) and bleomycin (BLM) were added to the medium directly; 4-nitroquinoline-1-oxide (4NQO) and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) were dissolved in dimethyl sulfoxide (DMSO). The dose response for the induction of acentric chromosome fragments was determined in neuroblasts of the embryos exposed in vitro to the four direct-acting chemicals, which are known to be mutagenic. After 1-hr exposure followed by a 3-hr recovery period (untreated cell cycle time is 4 hr) acentric fragments were observed at doses down to 1.0 uM 4NQO, 1.25 uM MNNG, and 0.125 uM ADM and BLM. With 4NQO, acentric fragments were induced at a dose as low as 0.125 uM after 8-hr continuous exposure. No chromosome aberrations or mitotic effects were observed in untreated embryos or those exposed only to DMSO. Comparison with other clastogen test systems currently used indicate that the grasshopper neuroblast test is the fastest and that it detects some agents that some other systems do not. (40 Refs)

51. A NOTE ON THE UTILITY OF REPAIR-DEFICIENT ST MUS302 DROSOPHILA FEMALES IN DETECTING CHROMOSOME LOSS AND SEX-LINKED RECESSIVE LETHALS INDUCED IN THE MALE GENOME BY METHYL METHANESULFONATE (MMS) AND DIMETHYLNITROSAMINE (DMN).

Zimmering S
Div. Biology and Medicine, Brown Univ., Providence, RI, 02912
Environ Mutagen; 4(3):291-293 1982

A study is presented which indicates that for the monofunctional alkylating agents methyl methanesulfonate and dimethylnitrosamine, the st mus302 test for chromosome loss is more sensitive than the mei-9a or conventional test (using repair-proficient females). The test is as sensitive as a sex-linked recessive lethal test treating Basc males and mating with st mus302 females. (7 Refs)

52. MUTATION ASSAY AT THE THYMIDINE KINASE LOCUS IN DIPLOID HUMAN LYMPHOBLASTS.

Liber HL, Thilly WG
(c/o Thilly) Genetic Toxicology Group, Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Mutat Res; 94(2):467-485 1982

Characterization of a thymidine kinase (TK) mutation assay was studied in WI-L2 human lymphoblasts and the response of the system to a variety of chemical mutagens is reported. The TK6 cell line could be mutated from TK+/- to TK-/- state by ethyl methanesulfonate, butyl methanesulfonate, nitrosomethylurea, UV light, ICR-191, 4-nitroquinoline oxide, fluorodeoxyuridine, benzo[a]pyrene, and aflatoxin B1, and was derived from HH4. TK6 contains approx 30% of the TK enzyme activity of the parent. (26 Refs)

53. ISOLATION OF UV-SENSITIVE MUTANTS OF MOUSE L5178Y CELLS BY A CELL SUSPENSION SPOTTING METHOD.

Shiomi T, Hieda-Shiomi N, Sata K
Div. Genetics, Natl. Inst. Radiological Sciences, 9-1, Anagawa 4, Chiba 260, Japan
Somatic Cell Genet; 8(3):329-345 1982

A new method is described for isolation of UV-sensitive mutants, which is applicable to cell lines growing in suspension, and which yields greater than 90% of highly UV-sensitive mutants. It is also useful in complementation assay. Fifty-six UV-sensitive mutants of L51 T/t mouse cells were isolated by the cell suspension spotting procedure after treatment with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG: 0.5, 1.0, or 1.5 ug/ml for 2 hr) or ethylmethane sulfonate (400 or 600 ug/ml for 18 hr). Mutagen-induced frequencies for highly UV-sensitive mutants were about 2-3x higher than those of 6-thioguanine-resistant (hypoxanthine phosphoribosyltransferase-negative) mutants. Four UV-sensitive mutants belonging to different complementation groups were examined for their sensitivity to killing by UV, 4-nitroquinoline-1-oxide, (4NQO) mitomycin C (CMMC), x-rays and MNNG. All four mutants were cross-sensitive to UV, 4NQO, and MMC, but not to x-rays, indicating that the cross-sensitivity might consist of at least four complementation groups. The method described is applicable to recovering more repair-deficient mouse cell mutants for studies of repair mechanisms. (47 Refs)

54. MUTAGENICITY AND SYNTHESIS OF ALPHA-SUBSTITUTED N-NITROSAMINES: DERIVATIVES WITH DITHIOCARBAMIC ACID.

Pool BL, Bertram B, Wiessler M
Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
Carcinogenesis; 3(5):563-567 1982

Disulfiram (DSF) can considerably alter the organotropy of chemical carcinogens. For N-nitrosodimethylamine and for N-nitrosodiethylamine the organotropy is shifted from the liver to the nasal cavity or the esophagus, respectively. Whereas the influence of DSF or its metabolites on enzyme systems has been studied, little is known about its interaction with the carcinogens at a molecular level. Therefore, postulated reaction products of a series of alpha-hydroxylated N-nitroso-dialkylamines and dithiocarbamate were synthesized and tested for mutagenicity in Salmonella typhimurium TA 1535. The results show that the compounds conjugated at a primary alpha-C-atom are not mutagenic, whereas those conjugated at a secondary alpha-C-atom are active. The primary N-nitroso-dithiocarbamates

represent unique examples of inactivated dialkyl-nitrosamine derivatives. In addition, their formation in vitro was indirectly demonstrated. The possible role these inactivated compounds may play during the DSF-modulation of carcinogenesis will be discussed. (Author abstract) (16 Refs)

55. MUTAGEN FORMATION AFTER THE ADDITION OF NITRITE TO NORMAL HUMAN GASTRIC JUICE.

Gatehouse DG, Tweats DJ
Genetic Toxicology Section, Histopathology Dept., Glaxo Group Res. Ltd., Park St., Ware, Hertfordshire, England
Carcinogenesis; 3(5):597-598 1982

The World Health Organization (WHO) has recently recommended the use of a simple in vitro test (Nitrosation Assay Procedure, NAP) to allow the ranking of orally administered drugs. It was suggested that the ranking of drugs should be carried out on a reactivity scale, according to their ability to nitrosate in the presence of high concentrations of nitrite at low pH (3-4). The present study was undertaken to investigate the effect of adding the concentration of nitrite recommended for the NAP test (40 mM) to normal fasting human gastric juice. The data clearly demonstrate that such treatment results in the formation of derivatives with specific mutagenic activity for the bacterium Salmonella typhimurium TA1537. This strain was recommended for use in the NAP Test. Although the NAP test may be valid for its original purpose, in the absence of more physiologically relevant data it is invalid for use as a final arbiter in risk-benefit assessments. The possible formation of mutagenic species as a result of the nitrosation of natural gastric secretions should be considered when any risk-benefit assessment is made. (Author abstract) (18 Refs)

56. HYPERSENSITIVITY OF ATAXIA TELANGIECTASIA SKIN FIBROBLASTS TO DNA ALKYLATING AGENTS.

Barfknecht TR, Little JB
Chemistry and Life Science Group, Res. Triangle Inst., Post Office Box 12194, Research Triangle Park, NC, 27709
Mutat Res; 94(2):369-382 1982

Three ataxia telangiectasia (AT) skin fibroblasts cells strains, AT4BI, AT5BI, and AT2BE (CRL 1343) were studied for survival following treatment with methyl methanesulfonate (MMS), ethyl methanesulfonate (EMS), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), and 4-nitroquinoline-1-oxide (4NQO) and results were compared to those obtained from three normal human fibroblast cell strains. None of the AT fibroblast strains were significantly more sensitive to MNNG treatment than the av normal survival. Similarly, no significant difference was observed in D10 values among the AT fibroblast strains and the normal av D10 value. Strain AT5BI appeared to be moderately sensitive to MMS treatment compared to the normal av survival. Comparison of the D0 value for strain AT5BI, 0.29 milliM (mM) vs the normal av of 0.38 +- 0.03 mM indicated a significant difference in the slope of the survival curve between strain AT5BI and the normal av survival curve. Strain AT4BI was hypersensitive to MMS treatment only when D0S were compared. All three fibroblast strains were significantly more sensitive to treatment with EMS than the normal controls. AT4BI, AT5BI, and AT2BE had D10S of 16, 13, and 15 mM, respectively, vs the normal human fibroblast av D10 value of 28 mM. AT4BI and AT2BE were abnormally sensitive to treatment with 4NQO as compared to the survival of the normal human fibroblast strains. (61 Refs)

CELLULAR EFFECTS OF NITROSO COMPOUNDS

57. A QUALITATIVE AND QUANTITATIVE ASSAY FOR CELLS LACKING POSTCONFLUENCE INHIBITION OF CELL DIVISION: CHARACTERIZATION OF THIS PHENOTYPE IN CARCINOGEN-TREATED SYRIAN HAMSTER EMBRYO CELLS IN CULTURE.

Nakano S, Bruce SA, Ueo H, Ts'o PO
(c/o Bruce) Div. Biophysics, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205
Cancer Res; 42(8):3132-3137 1982

We have developed a qualitative and quantitative assay system for detecting cells lacking postconfluence inhibition of cell division (contact insensitivity, CS-) in golden Syrian hamster embryo cells in culture by measuring the number of cells able to form colonies on a lethally irradiated, confluent monolayer of a contact-sensitive established cell line. A subpopulation in normal low-passage cultures of golden Syrian hamster embryo cells temporarily exhibits this CS- phenotype at very low frequency (approx 4 x 10(-3)) but quickly loses the property within a few passages in vitro. This phenotype is invariably exhibited by various tumorigenic cell lines at very high frequency (7 to 50 x 10(-2)) and appears to correlate with the anchorage-independent growth phenotype. The temporal acquisition of the CS- phenotype by tertiary-passage golden Syrian hamster embryo cells following exposure to N-methyl-N'-nitro-N-nitrosoguanidine was examined. Cells with a stably heritable CS- phenotype are detected after approx 20 posttreatment population doublings. In contrast, anchorage-independent cells are not detected until 35 to 95 posttreatment population doublings. These CS- cells appear to be preneoplastic cells, since clonally isolated CS- cells did not exhibit anchorage-independent growth until after further passaging in vitro. The results suggest that acquisition of the CS- phenotype represents an early stage in neoplastic progression. (Author abstract) (37 Refs)

58. INDUCTION OF NEOPLASTIC CELL GROWTH BY QUIESCENT CELLS IS MEDIATED BY SERUM CONCENTRATION AND CAMP PHOSPHODIESTERASE INHIBITORS.

Bertram JS, Bertram BB, Janik P
Grace Cancer Drug Center, Roswell Park Memorial Inst., Buffalo, NY, 14263
J Cell Biochem; 18(4):315-538 1982

Studies have shown that for transformed mouse fibroblasts (C3H/101/2) and Lewis lung carcinoma model systems, the expression of transformation is conditional upon the permissive behavior of neighboring cells. Such permissive behavior could be due to a failure in intercellular communication or to a failure in signal reception or processing. For a constant plating density an increase in serum concentration was shown to cause a dose responsive decrease in N-methyl-N-nitro-N-nitrosoguanidine (MNNG)-induced transformation frequency in fibroblast cells. This increase in serum concentration produced an increase in saturation density of confluent cells. A model is developed which suggests that interference in communication between cells occurs during transformation. The passage of small growth inhibitory substances through gap junctions between contacting cells controls cell cycle phase. Autonomous growth would occur through attenuation of signal intensity. This studies have identified two possible factors which may control signal strength, ie, cell density and elevated cAMP. The model

thus suggests that transformed cells are deficient in their ability to form communication channels with themselves or with adjacent normal cells. The major effect of phosphodiesterase inhibitors may be to increase the latent period between tumor injection and the appearance of tumor. Applications of the model to phosphodiesterase inhibitors and to tumor promotion are discussed. (42 Refs)

59. CYCLIC ADENOSINE 3':5'-MONOPHOSPHATE-DEPENDENT PROTEIN PHOSPHORYLATION AND THE CONTROL OF LEUKEMIA L1210 CELL GROWTH.

Mednieks MI, Jungmann RA, DeWys WD
Lab. Biological Structure, Natl. Inst. Dental Res., Building 30, Room 211, Bethesda, MD, 20205
Cancer Res; 42(7):2742-2747 1982

Synergistic increases in the survival of mice bearing an L1210 leukemia tumor have been demonstrated previously after treatment with 1,3-bis(2-chloroethyl)-1-nitrosourea together with theophylline over those treated with either agent alone. These results imply that manipulation of cyclic adenosine 3':5'-monophosphate (cyclic AMP) levels in L1210 cells may result in alteration of sensitivity to chemotherapy and alterations in tumor growth. In the present study, we have shown that in vivo treatment of L1210 cells with theophylline results in changes in intracellular cyclic AMP-dependent protein kinase activity levels as well as in an apparent redistribution of both the nuclear and cytoplasmic isozymes. Biochemical events in the tumor cells immediately after administration of theophylline in vivo or a cyclic AMP analog (8-parachlorophenylthio cyclic adenosine 3':5'-monophosphate) in vitro were independent of the presence of 1,3-bis(2-chloroethyl)-1-nitrosourea. The changes apparently involve signal transduction via the adenylate cyclase system and manifest as: (a) increased sensitivity of cyclic AMP-dependent protein kinase to activation by cyclic AMP after treatment of L1210 cells with theophylline; (b) decrease in endogenous nuclear protein phosphorylation sites; and (c) protein kinase isozyme redistribution between nuclear and extranuclear compartments, ie, a relative increase of the Type I isozyme activity in the nuclear and of the Type II isozyme activity in the 900 x g supernatant fractions after treatment of the mice of theophylline. The relative activity increases are accompanied by relative decrease of Type II activity from the nucleus and Type I isozyme activity from the 900 x g extranuclear supernatant fraction. These events appear temporally related to changes in nuclear RNA metabolism as evidenced by altered kinetics of RNA precursor uptake and incorporation into tumor cell RNA after treatment. These results imply that the cyclic AMP-dependent phosphorylative modification of intracellular proteins may play a regulatory role in tumor cell growth and in theophylline-mediated tumor regression. (Author abstract) (42 Refs)

60. MEASUREMENTS BY FILTER ELUTION OF DNA SINGLE- AND DOUBLE-STRAND BREAKS IN RAT HEPATOCYTES: EFFECTS OF NITROSAMINES AND GAMMA-IRRADIATION.

Bradley MO, Dysart G, Fitzsimmons K, Harbach P, Lewin J, Wolf G
Merck Inst. Therapeutic Res., West Point, PA, 19486
Cancer Res; 42(7):2592-2597 1982

This work presents a filter elution method for measuring DNA single- and double-strand breaks in primary rat hepatocytes without radioactive labeling of DNA. We have studied the effects of a series of nitrosamines and of gamma-irradiation on DNA single- and double-strand break induction. The repair of DNA single-strand breaks in the hepatocytes was measured after treatment with 60Co, 1-methyl-1-nitrosourea, and N-nitrosodimethylamine. The hepatocytes were isolated by ethylene glycol-bis(beta-aminoethyl ether)-N,N'-tetra acetic acid-collagenase perfusion and had a mean viability of 91 +-4% (SD). The isolated cells were treated for varying lengths of time with nitrosamines in suspension culture in L-15 medium containing 10% fetal bovine serum. After treatment, the cells were chilled, loaded onto 2-um polycarbonate filters, and lysed in a 2% sodium dodecyl sulfate-proteinase K solution, pH 9.6. The DNA was eluted from the filter at either native or denaturing pH with fractions collected every 3 hr. The quantity of DNA in each fraction was determined by measuring the fluorescent product formed between it and diaminobenzoic acid after ethanol-sodium acetate precipitation and trapping of the DNA on 0.2-um polycarbonate filters. The results show that the carcinogens, N-nitrosodimethylamine, N-nitrosodiethylamine, N-nitrosodipropylamine, N-nitrosodibutylamine, and 1-nitrosopiperidine all made dose- and time-related increases in the number of single-strand breaks in rat hepatocytes. N-Nitrosodiphenylamine produced small numbers of single-strand breaks. No double-strand breaks were formed by any of the nitrosamines. Single-strand breaks induced by N-nitrosodimethylamine were repaired very slowly relative to repair of either gamma-ray or 1-methyl-1-nitrosourea-induced single-strand breaks. This system has many advantages for studying carcinogen metabolism and DNA damage in hepatocytes, one of the major target cells for many carcinogens. (Author abstract) (19 Refs)

61. ALGINATE: A NEW REVERSIBLE GELLING MEDIUM FOR INVESTIGATING CELL TRANSFORMATION (MEETING ABSTRACT)

Roscoe JP, Owsianka AM
School of Pathology, Middlesex Hospital Medical School, London, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

Previous investigations of the malignant transformation of rat brain cells by ethylnitrosourea have shown that tumorigenic cells form colonies in agar. Furthermore, pre-neoplastic cells which do not form colonies nevertheless survive, but in an essentially non-dividing state, for much longer (up to 10 weeks) than control cells. Investigation of this phenomenon has been hampered by the technical difficulties of long term maintenance and recovery of cells suspended in methocel or agar. We have developed alginate as an alternative suspending medium from which viable cells can be recovered by disrupting the cation dependent linkages with a chelating agent. A base layer of 0.6% agar is allowed to set and the appropriate concentration of calcium chloride solution placed on top. Cells suspended in 1% sodium alginate are immediately overlaid resulting in the formation of a gel as the calcium ions react with the alginate. Cells can be released by addition of EDTA and collected by centrifugation. The results using this medium show that 1) tumorigenic and non-tumorigenic cells can be distinguished by colony forming ability in alginate 2) the difference in viability of pre-neoplastic and control cells found in agar can be reproduced with the advantage that the recovery over several weeks can be quantitated. (1 Ref)

62. REPAIR OF DNA ALKYLATION INDUCED IN L1210 LEUKEMIA AND MURINE BONE MARROW BY THREE CHLOROETHYLNITROSOUREAS.

Ahlgren JD, Green DC, Tew KD, Schein PS
Div. Medical Oncology, Georgetown Univ. Hosp., 3800 Reservoir Road, N.W., Washington, DC, 20007
Cancer Res; 42(7):2605-2608 1982

The removal of DNA adducts is an essential step of DNA repair following exposure to chloroethylnitrosoureas. Adduct removal was evaluated in both L1210 and murine bone marrow DNA for lesions induced by three chloroethylnitrosoureas. 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea, a marrow-toxic agent with high carbamoylating activity, was not removed in either system for at least 6 to 12 hr. These results were compared with those obtained with two glucose-linked chloroethylnitrosoureas, chlorozotocin and 1-(2-chloroethyl)-3-(beta-D-glucopyranosyl)-1 nitrosourea. Both of these agents have low marrow toxicity at therapeutic doses. Chlorozotocin, which has very low chemical carbamoylating activity, was found to permit approx 40% removal of drug-derived DNA adducts in both systems within the first 6 hr and approx 50% by 18 hr. The second glucose-linked analog, 1-(2-chloroethyl)-3-(beta-D-glucopyranosyl)-1 nitrosourea, has relatively high carbamoylating activity and was found to inhibit early removal of DNA adducts as effectively as does 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea. It would thus appear that the selective marrow-sparing property of the sugar-linked chloroethylnitrosoureas is not dependent upon carbamoylation-mediated differences in the rate and extent of DNA adduct removal. In view of the comparable therapeutic activity of the three drugs for L1210 leukemia, therapeutic efficacy does not appear to be impaired by the increased rate of adduct removal observed with chlorozotocin in this system. (Author abstract) (18 Refs)

63. HERITABLE ALTERATIONS IN TUMOR-CELL IMMUNOGENICITY.

Kerbel RS, Frost P
Dept. Pathology, Queen's Univ., Kingston, Ontario, Canada
Immunol Today; 3(2):34-36 1982

Heritable alterations in tumor-cell immunogenicity are discussed, with reference to recent studies in which strong mutagens such as N-methyl-n'-nitro-N-nitrosoguanidine and dacarbazine were used to induce immunologically more provocative mouse tumor cells. Xenogenizations seem likely to remain only an adjunctive therapy. (24 Refs)

TRANSPLACENTAL EFFECTS OF NITROSO COMPOUNDS

64. ULTRASTRUCTURAL FINDINGS IN SO-CALLED EPENDYMAL RAT TUMORS INDUCED BY TRANSPLACENTAL ADMINISTRATION OF ETHYLNITROSOUREA (ENU).

Mandybur TI, Alvira MM
Lab. Neuropathology, Dept. Pathology and Lab. Medicine, Univ. Cincinnati Coll. Medicine, 231 Bethesda Ave., Cincinnati, OH, 45267
Acta Neuropathol (Berl); 57(1):51-58 1982

CNS tumors induced by transplacental exposure to ethylnitrosourea (ENU) were studied in Sprague-Dawley and Lewis rats. A single dose of 10-25 mg/kg body wt was injected on days 16-19 of gestation. A total of 456 CNS tumors were induced in 328 rats of both sexes. According to current criteria 71 tumors could be classified as ependymomas, anaplastic ependymomas, or mixed tumors containing both oligodendroglioma and anaplastic ependymoma tissue components. Tumors were 1-6 mm in diameter and were located in the cerebral hemispheres, brain stem, cerebellum, and spinal cord. All tumors showed similar histological patterns, including a tendency towards cell aggregations (groups, clusters, cords, pseudoepithelial sheets, and pseudorosettes). Pseudorosettes showed polarization of the nuclei at the periphery; cytoplasm contained numerous polyribosomes, occasional short microtubules, and a few dense-core vesicles. At the center of pseudorosettes were interdigitating processes connected by maculae adherens and showing vesicular degeneration. Cells in cords or perivascular rosettes showed similar ultrastructure, but without polarization. All of the tumors examined lacked characteristics of true normal or neoplastic ependymal tissue, such as true rosettes, blepharoplasts, basal bodies, cilia, and complicated junctional complexes. Since tumors induced by ENU in the rat are evidently not true ependymal tumors but primitive neuroepithelial tumors with some characteristics of oligodendroglioma, criteria for classification should be revised. (16 Refs)

65. DIFFERENT RESULTS WITH TWO ASSAYS OF FIBRINOLYSIS AND THEIR CORRELATION WITH TUMORIGENICITY (MEETING ABSTRACT)

Fairbairn SR, Zammit-Pace R, Roscoe JP
School of Pathology, Middlesex Hospital Medical School, London, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

We have studied plasminogen-dependent fibrinolysis in cells derived at different times after transplacental exposure to the carcinogen ethylnitrosourea (ENU) or buffer. The cells were tested for fibrinolytic activity by two main methods: 1) lysis in a fibrin-agarose overlay of colonies, or 2) release of radioactivity from a layer of tritiated-fibrin seeded with whole cells. Cell lines which were tumorigenic immediately they were derived showed increased fibrinolytic activity in both assays when compared with control lines. However, some of these lines could lose their fibrinolytic activity as measured by the radioactive method while remaining positive in the overlay assay, tumorigenic and able to form colonies in agar. Cell lines derived soon after ENU exposure also developed increasd fibrinolytic activity measured by the overlay method and later could grow in agar or animals. However, latent period cultures showed low, slightly elevated or variable values of fibrinolysis in the radioactive assay. A comparison of the two assay methods suggested that differences in culture conditions, such as the time of medium change, may cause the difference in results. Fibrinolysis by those cells which were positive in the overlay assay and not in the radioactive assay, was reduced if the cells were incubated with fresh medium containing serum immediately before being overlaid. However, those cells which were positive in both assays were not affected by this treatment. (no Refs)

IMMUNOLOGICAL AND VIROLOGICAL ASPECTS OF NITROSO COMPOUNDS

66. CARCINOGEN-MEDIATED AMPLIFICATION OF SPECIFIC DNA SEQUENCES.

Lavi S
Dept. Virology, Weizmann Inst. Science, Rehovot, Israel
J Cell Biochem; 18(2):149-156 1982

The development of a experimental system model , which utilizes simian virus 40 (SV40)-transformed Chinese hamster embryo cells, coupled with a highly sensitive in situ hybridization procedure for the detection of a single cell in which viral DNA synthesis has been induced, is presented. When exposed to chemical carcinogens such as benzo(a)pyrene, N-methyl-N'-nitro-N-nitrosoguanidine, 7,12-dimethyl benz(a)anthracene (DMBA), ethyl methanesulfonate, aflatoxin B1, and 3-methylcholanthrene or physical carcinogens (gamma or UV radiation), SV40 DNA synthesis was induced in treated cells. Noncarcinogenic compounds such as phenanthrene and dibenz(a,c)anthracene had no effect. While carcinogen-induced amplification of SV40 DNA sequences is controlled by the viral 'A' gene, no infectious virus or complete SV40 DNA molecules were found in treated cells. DMBA treatment induced a heterogenous collection of DNA molecules with SV40 sequences. Analysis of Hirt's supernatant using restriction enzyme analysis of the amplified DNA molecules indicated that not all sequences in the integrated SV40 inserts are present. Amplification of SV40 DNA sequences may reflect a more general gene amplification phenomenon mediated by chemical carcinogens. (19 Refs)

67. DIFFERENTIAL EFFECTS OF HYDROXYUREA ON THE SURVIVAL OF UV- AND MNNG-TREATED ADENOVIRUS 5.

Day RS, Ziolkowski CH
Nucleic Acid Section, LMC, DCCP, NCI, NIH, Building 37, Room 3C23, Bethesda, MD, 20205
Mutat Res; 94(2):257-262 1982

Effects of hydroxyurea (HU) on the survival of both UV- and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) treated adenovirus 5 when used to infect either human cell strains XP12BE, CRL1220, XP4BE, and KD were studied and it was observed that HU decreased in all cases studied the survival of UV-irradiated adenoviruses. A 24-hr 10-milliM (mM) HU post-infection treatment of XP12BE fibroblasts caused apparent increase in sensitivity of UV-irradiated adenovirus 5. The magnitude of inhibition of viral recovery by HU, however, was less than that observed when infecting normal fibroblasts. In the presence of HU, the lethality of a given dose was increased by a factor of 2.1 in normal, cells, and by 1.29 using the XP12BE strain. In ancillary experiments, 10 mM HU present with KD cells only during the 24 hr prior to infection caused no enhancement of viral inactivation. HU (10 mM) applied to CRL1187 or KD normal fibroblasts (Mer+) infected with MNNG-treated adenoviruses caused no change in viral survival indicating that HU dose not interfere greatly with the Mer repair pathway. However, HU treatment did increase the survival of MNNG-treated viruses when infecting the A1336 and A172 Mer- strains, the lethality of a given dose being increased by 1.52 +-0.10. The result showed that viral recovery occuring independently of the Mer system is somewhat susceptible to blockage by the HU treatment. (26 Refs)

68. DETECTION OF TUMOR ANTIGENS BY SYNGENEIC ANTISERUM ON IN VITRO-TRANSFORMED TRACHEAL EPITHELIAL CELL LINE 2-10-1.

Braslawsky GR, Kennel SJ, Steele V, Nettesheim P
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Int J Cancer; 29(6):677-681 1982

Sera obtained from rats showing transplantation immunity to syngeneic, malignant epithelial cell line, 2-10-1, were used to identify antigens associated with transformation in vitro. The 2-10-1 cell line was derived from exposure of tracheal explants, in vitro, to the carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). Tumorigenic passages of the cell line were shown to have common antigenic determinants, shared by independently transformed malignant tracheal epithelial cell lines, as well as antigenic determinants that appear to be limited to the immunizing cell line, 2-10-1. Care was taken to ensure that antibodies were not produced against viral antigens or non-specifically absorbed serum components. Early passages of the 2-10-1 cell line were not tumorigenic in athymic BALB/c (nu/nu) mice, but became malignant with serial passage in vitro. Antigenic specificities recognized by 2-10-1 immune sera were also present on early-passage 2-10-1 cells that had not as yet acquired the malignant phenotype. Such antigen expression must be an early event in neoplastic development. (Author abstract) (20 Refs)

EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS

69. MUTAGENS IN HUMAN FAECES. ARE THEY RELEVANT TO CANCER OF THE LARGE BOWEL?

Venitt S
Chester Beatty Res. Inst., Nightingales Lane, Chalfont St. Giles, Bucks HP8 4SP, England
Mutat Res; 98(3):265-286 1982

Bacterial mutation studies and cytogenetic studies of extracts of human feces (HF) and the role of mutagens in HF are reviewed. The hypothesis that colorectal cancer might be caused by carcinogenic chemicals generated endogenously by metabolism of fecal substrates by the gut microflora has been tested directly, using short-term assays which have been developed for detecting potential carcinogens. Studies on nitrate, nitrite, and nitrosamines in the intestinal tract (IT) showed that conditions in the lower IT favor denitrification rather than nitrification. Bacterial mutagens have been detected in fecal extracts obtained from several groups of subjects drawn from widely differing communities and consuming very different diets. Chromosome-damaging activity has also been demonstrated in extracts of HF, this latter finding being based on a very small sample group. Therefore, studies indicate that normal people regularly excrete feces which contains constituents possessing properties (mutagenicity and clastogenicity) characteristic of carcinogens. The possibility that the mutagenic activity of fecal extracts is artefactual cannot be excluded until extraction and mutagenesis assays are preformed under anaerobic conditions. Apart from the metabolic activity of fecal flora occupying the colonic lumen, the colonic epithelium itself possesses enzyme systems capable of metabolizing xenobiotics to mutagenic derivatives. The complex interaction between dietary fiber, transit time, and the frequency of bowel movements must also play

a part in modifying the response of the colonic epithelium to continuous assaults by fecal mutagens. The protective mechanisms would operate within certain upper limits, which, if exceeded, would be expected to allow reversible or irreversible damage to occur to molecular and cellular components of the mucosa. (58 Refs)

70. THE ROLE OF DIETARY FIBER IN LIPID METABOLISM.

Story JA
Dept. Foods and Nutrition, Purdue Univ., West Lafayette, IN
Adv Lipid Res; 18:229-246 1981

The interaction of dietary fiber in lipid metabolism and in lipid-associated disease is discussed. In spite of strong relationships indicated by epidemiological studies, little is known concerning the mechanisms involved and details concerning specific types of dietary fibers involved. The magnitude of the interaction between some types of dietary fiber and bile acids appears sufficient to result in an alteration of bile acid excretion and, as a result, alter sterol balance. At the same time, a resultant increase in concentration of bile acids in the colon may be related to susceptibility to colon carcinogenesis. In one experimental study, the feeding of three types of dietary fiber (alfalfa, cellulose, or bran) led to significantly reduced colon tumors induced by azoxymethane (AOM) when dietary fat was reduced from 35% to 7%. Another study involving use of AOM and intrarectal instillation of methylnitrosourea and various dietary fibers indicated that those fibers which result in dilution of bile acids (eg, bran, cellulose) result in the most consistent reduction in chemically induced colon tumors. (67 Refs)

71. AETIOLOGICAL ASPECTS OF BLADDER CANCER IN URINARY BILHARZIA.

Mee AD
Urology Unit, Royal Postgraduate Medical Sch., Hammersmith Hosp., London, England
Saudi Med J; 3(2):123-128 1982

The etiology of urinary bladder cancer (BC) is discussed in relation to bilharzia, the incidence of which is much higher in Egypt than in Saudi Arabia. Beta-glucuronidase in the urine has been linked to BC, increased levels of which occur in patients with urinary infections caused by Escherichia coli and Pseudomonas, which are common causes of secondary infections in urinary bilharziasis. However, experimentally, this enzyme has not been proven to be a significant bladder carcinogen. There is experimental evidence that nitrosamines which may form in the urine of some people produce BC. Variations in dietary nitrate could account for the low incidence of BC in the Arabian peninsula and the higher incidence in Egypt. Egyptian farmers have a higher incidence of BC as a complication of bilharzia than professional and business classes. There was also a greater incidence of nitrosamines in the urine of patients with BC and bilharzia than in patients with other cancers of the bladder alone or in patients with bilharziasis alone. The results were not conclusive that nitrosamines were the precipitating cause. The possible role of immunocompetence in urinary bilharziasis is discussed. The present study indicates that carcinoma of the bladder in patients with urinary bilharziasis is due to several factors including carcinogens in the urine of the bladder, and depressed immunocompetence caused by schistosoma antigen. (21 Refs)

72. DRUG-NITRITE INTERACTIONS IN HUMAN SALIVA: EFFECTS OF FOOD CONSTITUENTS ON CARCINOGENIC N-NITROSAMINE FORMATION.

Rao GS, Osborn JC, Adatia MR
Div. Biochemistry, Lab. Pharmacology, Res. Inst., American Dental Association Health Foundation, Chicago, IL, 60611
J Dent Res; 61(6):768-771 1982

A simple and rapid high-pressure liquid chromatographic assay for monitoring N-nitrosodimethylamine (NDMA) in human saliva was developed. The method was used to study in vitro the effects of common food constituents on NDMA formation in saliva from the interaction of salivary nitrite with aminopyrine and oxytetracycline. Natural phenolic compounds, caffeic acid, and tannic acid, and synthetic additives, erythorbic acid, sorbic acid, propyl gallate, and butyrated hydroxytoluene - all inhibited NDMA formation (20-80%). With ascorbic acid, up to 90% inhibition of NDMA synthesis in saliva was observed. In contrast, chlorogenic acid (a phenolic component of coffee) acted as a catalyst (up to 48% increase) of the nitrosamine formation under identical experimental conditions. (Author abstract) (21 Refs)

73. INHIBITION OF N-NITROSAMINES IN BACON.

Gray JI, Reddy SK, Price JF, Mandagere A, Wilkens WF
Dept. Food Science and Human Nutrition, Michigan State Univ., East Lansing, MI, 48824
Food Technol; 36(6):39-45 1982

Mechanisms of N-nitrosamine formation during cooking of bacon, approaches to reduction of N-nitrosamine levels, and inhibition of N-nitrosation reactions are reviewed, and the applicability and effectiveness of alpha-tocopherol-coated salts in inhibiting N-nitrosamine formation in both dry-cured and brine-cured bacons are discussed. Alpha-tocopherol-coated salt systems are very effective inhibitors of N-nitrosamine formation in fried bacon, and do no affect the safety of the product or the antibotulinal activity of nitrite. (38 Refs)

74. INFLUENCE OF NITRATES ON THE HEALTH STATUS OF THE POPULATION.

Vondrakova M
Institut hygieny a epidemiologie, Srobarova 48, 100 42 Prague 10, Czechoslovakia
Cesk Hyg; 27(3):162-172 1982

Studies on the health effects of nitrates and nitrites are reviewed. Nitrates and nitrites possibly participate in the formation of carcinogenic N-nitroso compounds (N-nitrosodimethylamine, N-nitrosodiethylamine, N-nitrosopyrrolidone and N-nitrosopiperidine) in foods and organisms. Recent epidemiological studies show a correlation between the incidence of carcinoma of certain localizations (especially of the stomach) and the presence of nitrosamines, nitrates and nitrites in the environment. (80 Refs) (In CZE)

75. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME AROMATIC AMINES, ANTHRAQUINONES AND NITROSO COMPOUNDS, AND INORGANIC FLUORIDES USED IN DRINKING-WATER AND DENTAL PREPARATIONS.

IARC Working Group
International Agency for Research on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 27:1-7 1982

Monographs on carcinogenicity data for groups of chemicals to which humans are known to be exposed are presented, and some aromatic amines and anthraquinones (used mainly as dyestuff intermediates), two nitroso compounds, and inorganic fluorides used in the fluoridation of drinking water or in dental preparations are included. The importance of data on the purity of chemicals used in animal carcinogenicity experiments and in mutagenicity tests was emphasized. Aromatic amines discussed include aniline and aniline hydrochloride, ortho-anisidine and para-anisidine and their hydrochlorides, 4-chloro-ortho-phenylenediamine and 4-chloro-meta-phenylenediamine, meta-cresidine and para-cresidine, 2,4-diaminoanisole and 2,4-diaminoanisole sulfate, 4,4'-methylenebis(N,N-dimethyl)benzenamine, 1,5-naphthalenediamine, 2,2',5,5'-tetrachlorobenzidine, 4,4'-thiodianiline, ortho-toluidine and ortho-toluidine hydrochloride, and 2,4,5-trimethylaniline and 2,4,6-trimethylaniline and their hydrochlorides. Anthraquinones include 2-aminoanthraquinone, 1-amino-2-methylanthraquinone, and 2-methyl-1-nitroanthraquinone. Nitroso compounds include N-nitrosodiphenylamine and para-nitrosodiphenylamine. An appendix on the epidemiological evidence relating to the possible carcinogenic effects of hair dyes in hairdressers and users of hair dyes is included. Critical analyses of the data presented are made in order to assist national and international authorities in formulating decisions concerning preventive measures. (744 Refs)

REVIEWS INCLUDING NITROSO COMPOUNDS

76. INHIBITION OF TUMOR INDUCTION AND DEVELOPMENT.

Zedeck MS, Lipkin M
Memorial Sloan-Kettering Cancer Center, New York, NY
Inhibition of Tumor Induction and Development. New York, Plenum Press, 233 pp., 1981.

Major aspects of chemoprevention, focusing on the inhibition of carcinogen formation, absorption, and metabolic activation and interaction with cell macromolecules, as well as prevention through immunological approaches, are outlined. Inhibition of chemical carcinogenesis by phenols, coumarins, aromatic isothiocyanates, flavones, and indoles and inhibition of carcinogen metabolisms and action by disulfiram, pyrazole, and related compounds are discussed. Retinoids and chemoprevention of cancer; ascorbic acid inhibition of N-nitroso compound formation in chemical, food, and biological systems; alpha-tocopherol and its relationship to tumor induction and development; trace elements and metals as anticarcinogens; and the protective role of plant sterols in chemical carcinogenesis are described. Immunoprevention is discussed with respect to detection of tumor-associated antigens in experimental rat bowel carcinomas, evidence that embryonic antigens are associated with bowel carcinomas, enhanced 1,2-dimethylhydrazine (DMH)-induced tumorigenesis in imunosuppressed rats, inhibitory effect on bowel carcinogenesis by immunization with transplantable syngeneic colon carcinoma and by immunization with fetal tissue, inhibition of DMH-induced carcinogenesis in multiparous rats, effects of tumor resection on the development of additional primary tumors, and regression of early primary bowel carcinomas by multimodal immunological treatment are discussed. (738 Refs)

77. METABOLIC EPIDEMIOLOGY OF LARGE BOWEL CANCER.

Hill MJ
Central Public Health Lab., Colindale Ave., London NW9, England
Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

The epidemiology of large bowel cancer and predisposing and associated diseases are reviewed. Possible causative agents, evidence for the role of bile acids as co-carcinogens, and metabolic epidemiology vis results of studies of the histopathology of large bowel cancer and the adenoma-carcinoma sequence are considered. Variables examined in relation to the development of large bowel cancer include geography, sex, socioeconomic group, race, religion, population density, time and cultural environment. Predisposing diseases include adenomatosis coli, cancer family syndrome, and colorectal adenoma. Associated diseases include associated cancers, diseases of fiber depletion, and others. Possible causative agents are stress and physical factors, radiation, immunological factors, virological factors, environmental agents, endogenous agents (cholesterol, bile acids, steroid estrogens, tryptophan metabolites, tyrosine metabolism, and N-nitroso compounds), nutrition, and genetic factors. (154 Refs)

78. CANCER OF THE GASTRIC STUMP.

Dahm K
Univ. Hosp. Hamburg, Martinistrasse 52, 2000 Hamburg 20, W. Germany
Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

Cancer of the gastric stump (CGS) is reviewed. Topics include the interval between resection for ulcer and manifestation of CGS, epidemiology, occurrence (autopsy and follow-up studies), etiology (duodenogastric reflux and development of CGS, development of N-nitroso compounds in the gastric stump, relationship of type of ulcer disease and CGS), diagnosis and therapy (clinical and diagnostic symptoms, endoscopy, radiologic examination, surgical therapy), pathology (macroscopic findings; localization; microscopic findings for polyps, intestinalization, lipid islands, dysplasia, and atrophic gastritis), and experimental CGS. (80 Refs)

79. INHALATION CARCINOGENESIS: AN OVERVIEW.

Chretien J
Hopital Laennec, 42 rue du Sevres, F-75007 Paris, France
Recent Results Cancer Res; 82:1-10 1982

Environmental carcinogens and their site specific action under conditions of inhalation are considered. The main carcinogens to which man is currently known to be exposed, their mode of penetration, and the histological types of carcinoma they produce are listed. Carcinogens identified in tobacco smoke include dimethylnitrosamine, diethylnitrosamine, methylethylnitrosamine, N-nitrosopyrolidine, nitrosopiperidine,

benzo(a)pyrene, methylbenzo(a)pyrene, dibenz(a,h)acridine, dibenz(a,j)acridine, dibenz(c)carbazole, Beta-naphthylamine, benzo(b)fluoranthene, benzo(j)fluoranthene, methylfluoranthene, benzo(a)anthracene, chrysene, methchrysenes, and benzo(c)phenanthrene. A complex aerosol like tobacco smoke is particularly oncogenic due to synergism between components, small size of particles, and the repetitive nature of the exposure. The list of chemical environmental inhaled carcinogens will undoubtedly grow. Difficulties experienced in the detection of environmental carcinogens are discussed. Mechanisms implicated in carcinogenesis at respiratory surfaces are briefly reviewed. (45 Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Adatia MR 72
Ahlgren JD 62
Alvira MM 64
Arafah BM 27
Arai Y 7
Archer MC 2
Archer MC 8
Aulika BV 23
Barfknecht TR 56
Bartsch H 37
Bertram B 54
Bertram BB 58
Bertram JS 58
Biegel JA 46
Biegel JA 47
Biggs D 48
Billings PC 45
Bishop WW 33
Boggs SS 46
Boggs SS 47
Bradley MO 60
Braslawsky GR 68
Brittebo EV 12
Brodie AM 26
Brown CA 21
Bruce SA 57
Bushinskaia LI 23
Camus AM 37
Carpenter DA 35
Cave WT 29
Chasko JH 1
Chouroulinkov I 49
Chretien J 79
Conner MK 46
Conner MK 47
Cornett CV 35
Croisy A 37
Dahm K 78
Day RS 67
DeCosse JJ 18
DeWys WD 59
Deschner EE 18
Dolinskaia SI 23
Douglas GR 48
Downing M 32
Dysart G 60
El-Bayoumy K 9
Erickson-Lucas 29
Evarts RP 21
Fairbairn SR 65
Falchuk KR 33
Fiala E 9
Fitzsimmons K 60
Flaks A 16
Flaks B 16
Flavell DJ 17
Ford GP 4
Friesen M 37
Frost P 63
Furukawa K 11
Garrett WM 26
Gatehouse DG 55
Gaulden ME 50
Gentil A 49
Gombar CT 19
Goth-Goldstein 41
Gray JI 73
Green DC 62
Guinn GM 35
Gupta RS 44
Hamashima Y 15
Harbach P 60
Hecht SS 36
Hecht SS 9
Heidelberger C 45
Hemminki K 10
Hendrickson JR 26
Hieda-Shiomi N 53
Hill MJ 77
Hodgson RM 3
Huh N 38
Hunsicker PR 34
Hunsicker PR 35
IARC Working Gr 75
Iakimova ER 23
Iwata C 31
Janik P 58
Jungmann RA 59
Kawamori M 7
Kawasaki H 30
Kennel SJ 68
Kerbel RS 63
Kieffer JD 32
Kimoto E 30
Kirk MC 42
Kleihues P 3
Konstantinidis 14
Konstantinova I 23
Kwok SE 48
Labuc GE 2
Labuc GE 8
Larson RE 5
Lavi S 66
Lewin J 60
Liang JC 50
Liber HL 52
Lipkin M 76
Little JB 56
Litvinov NN 23
Lofberg B 12
Ludlum DB 42
Lum KL 28
Magee PN 19
Maloof F 32
Mandagere A 73
Mandybur TI 64
Manni A 27
Matsui I 24
McCormick DL 25
McCoy EC 36
McCoy GD 36
Mednieks MI 59
Mee AD 71
Mendel J 43
Merkur'eva RV 23
Miyazaki K 15
Mochizuki Y 11
Moldowan MJ 5
Moon RC 25
Moore MA 16
Morikawa T 7
Morishige F 30
Mostafa MH 21
Mover H 32
Mukhambetova LK 23
Murota T 39
Murota T 40
Nakano S 57
Nemeth P 20
Nemoto N 38
Nettesheim P 68
Okamura T 18
Osborn JC 72
Owsianka AM 61
Ozeki M 7
Parks NJ 1
Pearson OH 27
Pegg AE 24
Poirier LA 6
Pool BL 54
Price JF 73
Puju S 33
Rainieri J 27
Raj HG 6
Rao GS 72
Raymer GD 34
Reddy SK 73
Renault G 49
Reznik-Schuller 13
Ridgway EC 32
Rivenson A 9
Roscoe JP 61
Roscoe JP 65
Russell WL 34
Russell WL 35
Salmon RJ 18
Sata K 53
Schein PS 62
Schneider J 20
Schwarz H 43
Schweinsberg F 3
Scribner JD 4
Sherlock P 18
Shibuya T 39
Shibuya T 40
Shiomi T 53
Shuker DE 33
Singh B 44
Smith GP 22
Smulow JB 14
Sonnenschein C 14
Steele MH 34
Steele V 68
Stelzner KF 34
Story JA 70
Swartz LA 1
Takasan H 15
Tanaka H 30

Tannenbaum SR..... 33
Tew KD..... 62
Thayer JR..... 1
Thilly WG..... 33
Thilly WG..... 52
Thompson HM..... 34
Thust R..... 43
Tjaive H..... 12
Tomkins DJ..... 48
Tong WP..... 42
Ts'o PO..... 57
Tsai-Morris CH..... 26
Tsujihara K..... 7
Tutikawa K..... 39
Tutikawa K..... 40
Tweats DJ..... 55
Ueo H..... 57
Umino N..... 7
Utakoji T..... 38
Vainio H..... 10
Venitt S..... 69
Vickery AL..... 32
Vondrakova M..... 74
Votiakov AV..... 23
Warzok R..... 20
Wiessler M..... 3
Wiessler M..... 54
Wilkens WF..... 73
Williams AE..... 22
Wilson VL..... 5
Wolf G..... 60
Zammit-Pace R..... 65
Zedeck MS..... 76
Zimmering S..... 51
Ziolkowski CH..... 67

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICITY OF POLYBROMINATED BIPHENYLS (PBBS) IN DOMESTIC AND LABORATORY ANIMALS.

Damstra T, Jurgelski W, Posner HS, Vouk VB, Bernheim NJ, Guthrie J, Luster M, Falk HL
Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC, 22709
Environ Health Perspect; 44():175-188 1982

2. CHLOROFORM: A REVIEW OF ITS METABOLISM, TERATOGENIC, MUTAGENIC, AND CARCINOGENIC POTENTIAL.

Davidson IW, Sumner DD, Parker JC
(c/o Parker) ECAO, Environmental Protection Agency, MD-52, Research Triangle Park, MD, 27711
Drug Chem Toxicol; 5(1):1-87 1982

3. FORMALDEHYDE IN PRESENT-DAY ENVIRONMENTAL TOXICOLOGY.

Beritic T, Kovac S, Dimov D
Odjel za profesionalne bolesti, Institut za medicinska istrazivanja i medicinu rada, Zagreb, Yugoslavia
Arh Hig Rada Toksikol; 32(4):363-395 1981
In SCR

4. HORMONES AS ETIOLOGICAL AGENTS IN NEOPLASIA.

Furth J
Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

5. CURRENT VIEWS ON HORMONES AND BREAST CANCER.

Molinatti GM, Limone P
Cattedra di Endocrinologia, Universita di Torino, C.so Polonia, 14, 10126 Turin, Italy
Minerva Med; 73(17):1047-1053 1982
In ITA

6. THE CHROMOSOMAL EFFECTS OF THE ORAL CONTRACEPTIVE.

Bishun NP
Tissue Culture and Cytogenetics Unit, Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey, England
J Surg Oncol; 20(2):115-118 1982

7. TOXICITY AND CARCINOGENICITY OF NICKEL AND ITS COMPOUNDS. A REVIEW OF THE CURRENT STATUS.

Raithel HJ, Schaller KH
Institut fur Arbeits- und Sozialmedizin, Poliklinik fur Berufskrankheiten, Universitat Erlangen-Nurnberg, Schillerstrasse 25-29, D-8520 Erlangen, W. Germany
Zentralbl Bakteriol Mikrobiol Hyg [B]; 173(1/2):63-91 1981
In GER

8. HISTORICAL OVERVIEW OF NITROSOUREA DEVELOPMENT.

Goldin A
Div. Cancer Treatment, NCI NIH, Building 37, Room 5E20, Bethesda, MD, 20205
INSERM Symp; 19:3-11 1981

9. PATHOLOGY.

Goyer RA
Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC
JAMA; 247(21):2973-2975 1982

RADIATION CARCINOGENESIS

10. IDENTIFYING THE HEALTH RISKS FROM VERY LOW-DOSE SPARSELY IONIZING RADIATION.

Dreyer NA, Friedlander E
Epidemiology Resources, Inc., P.O. Box 57, Chestnut Hill, MA, 02167
Am J Public Health; 72(6):585-588 1982

11. RISK OF RADIOLOGICAL EXAMINATIONS.

Jankowski J
Instytut Medycyny Pracy w Lodzi, ul. Olowiana 6, 91-614 Lodz, Poland
Pol Przegl Radiol; 45(6):383-386 1981
In POL

12. RADIOBIOLOGY OF RISK ESTIMATES IN MEDICAL IRRADIATION (MEETING ABSTRACT)

Rossi HH
Columbia University, New York, NY
IN: 148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C American Association for the Advancement of Science 182 pp., 1982.

13. RADIATION-INDUCED VASCULAR INJURY AND ITS RELATION TO LATE EFFECTS IN NORMAL TISSUES.

Law MP
MRC Cyclotron Unit, Hammersmith Hosp., London W12 OHS, England
Adv Radiat Biol; 9:37-73 1981

14. CURRENT CONCEPTS IN ULTRAVIOLET CARCINOGENESIS.

Granstein RD, Sober AJ
(c/o Sober) Dept. Dermatology, Massachusetts General Hosp., Boston, MA, 02114
Proc Soc Exp Biol Med; 170(2):115-125 1982

15. METABOLIC CHANGES AFTER EXPOSURE TO RADIONUCLIDES.

Kalistratova VS
No affiliation given
Med Radiol (Mosk); 27(4):62-71 1982
In RUS

DIETARY FACTORS IN CARCINOGENESIS

16. CAFFEINE: AN UPDATE.

Oser BL, Ford RA
Bernard L. Oser and Associates, 108-18 Queens Blvd., Forest Hills, NY, 11375
Drug Chem Toxicol; 4(4):311-329 1981

17. ANALYSIS OF MUTAGENIC EFFECTS OF FOREIGN SUBSTANCES IN THE FOOD PRODUCTS.

Maganova NB
Inst. Nutrition, Moscow, USSR
Vopr Pitan; (2):3-8 1982
In RUS

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

18. RADIATION EPIDEMIOLOGY (MEETING ABSTRACT)

Marks S
No affiliation given
148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C. American Association for the Advancement of Science 182 pp., 1982.

19. EPIDEMIOLOGICAL STUDIES ON RADIATION CARCINOGENESIS IN HUMAN POPULATIONS FOLLOWING ACUTE EXPOSURE: NUCLEAR EXPLOSIONS AND MEDICAL RADIATION.

Fabrikant JI
Donner Lab., Univ. California, Berkeley, CA, 94720
Yale J Biol Med; 54(6):457-469 1981

20. EPIDEMIOLOGIC APPROACH TO CANCER.

Guinee VF
Dept. Epidemiology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

21. EPIDEMIOLOGY AND EARLY DETECTION OF CANCER OF THE ESOPHAGUS.

Sorouri P
900 Hillside Road, Wilmington, DE, 19807
Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

22. METABOLIC EPIDEMIOLOGY OF LARGE BOWEL CANCER.

Hill MJ
Central Public Health Lab., Colindale Ave., London NW9, England
Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

23. EPIDEMIOLOGY OF GASTRIC CANCER AND ITS PRECURSOR LESIONS.

Correa P
Louisiana State Univ. Medical Center, New Orleans, LA, 70112
Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

24. TRENDS IN THE INCIDENCE OF GASTRIC CARCINOMA (MEETING ABSTRACT)

Nobrega FT
Preventive and Internal Medicine, Mayo Clinic, Rochester, MN
Eleventh Annual William Beaumont Gastrointestinal Symposium, March 24-26, 1982, El Paso, Texas. William Beaumont Army Medical Center 56 pp., 1982.

25. CANCER IN INFLAMMATORY BOWEL DISEASE.

Bayless TM, Yardley JH
Johns Hopkins Hosp., Baltimore, MD, 21205
Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

26. GENETIC ASPECTS OF GUT CANCER.

McConnell RB
Broadgreen Hosp., Liverpool, England
Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

27. HOST AND ENVIRONMENTAL FACTORS ENHANCING CARCINOGENESIS IN THE RESPIRATORY TRACT.

Nettesheim P, Topping DC, Jamasbi R
Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709
Annu Rev Pharmacol Toxicol; 21:133-163 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

28. A SEARCH FOR SAFE DRINKING WATER.

Hairsine MA, Schumm HA
Northern Indiana Health Systems Agency, Inc., South Bend, IN
A Search for Safe Drinking Water. Available from National Technical Information Service, Springfield, VA, as HRP-0903845/6:, 68 pp., 1981.

29. OCCUPATIONAL EXPOSURES TO URANIUM: PROCESSES, HAZARDS, AND REGULATIONS.

Stoetzel GA, Fisher DR, McCormack WD, Hoenes GR, Marks S
Battelle Pacific Northwest Lab., Richland, WA
Occupational Exposures to Uranium: Processes, Hazards, and Regulations. Available from National Technical Information Service, Springfield, VA, as PNL-3341-USUR-01:, 91 pp., 1981.

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

30. THE ROLE OF RADIATION AND CHEMICALS IN THE INDUCTION OF MUTATIONS AND EPIGENETIC CHANGES DURING CARCINOGENESIS.

Trosko JE, Chang CC
Dept. Human Development, Coll. Human Medicine, Michigan State Univ., East Lansing, MI, 48824
Adv Radiat Biol; 9:2-36 1981

31. SOME EFFECTS OF CARCINOGENS ON CELL ORGANELLES.

Svoboda DJ, Reddy J
Dept. Pathology and Oncology, Univ. Kansas Coll. Health Sciences, Kansas City, KS
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

32. CHEMICAL CARCINOGENESIS: INTERACTIONS OF CARCINOGENS WITH NUCLEIC ACIDS.

Rajalakshmi S, Prema M, Sarma D
Dept. Pathology, Univ. Toronto, Toronto, Ontario, Canada
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

33. A MOLECULAR RATIONALE FOR NITROSOUREA INDUCED CYTOTOXICITY.

Tew KD
Lombardi Cancer Center, Div. Medical Oncology, Georgetown Univ., 3800 Reservoir Road, N.W., Washington, DC, 20007
INSERM Symp; 19:61-77 1981

34. MODIFICATION OF DNA AND RNA BASES BY THE NITROSOUREAS.

Ludlum DB, Tong WP
Div. Oncology, Dept. Pharmacology and Experimental Therapy, Albany Medical Coll., Albany, NY, 12208
INSERM Symp; 19:21-31 1981

35. CALMODULIN AND CA2+ IN NORMAL AND TRANSFORMED CELLS.

Veigl ML, Sedwick WD, Vanaman TC
Dept. Microbiology and Immunology, Duke Univ. Medical Center, Durham, NC, 27710
Fed Proc; 41(7):2283-2288 1982

36. METABOLISM AND TOXICITY OF AFLATOXINS.

Hsieh DP, Wong JJ
Dept. Environmental Toxicology, Univ. California, Davis, Davis, CA, 95616
Adv Exp Med Biol; 136(partB):847-863 1982

37. REACTION OF MICROSOMAL AND CYTOSOLIC ENZYMES WITH N-ARYLACETOHYDROXAMIC ACIDS IN THE PRESENCE OF OXYGEN.

Lenk W, Scharmer U
Pharmakologisches Institut, Universitat Munchen, Nussbaumstrasse 26, D-8000 Munchen 2, W. Germany
Adv Exp Med Biol; 136(partB):951-970 1982

38. METABOLIC ACTIVATION AND DEACTIVATION MECHANISMS OF DI-, TRI-, AND TETRACHLOROETHYLENES.

Henschler D, Hoos R

Inst. Toxicology, Univ. Wurzburg, Versbacher Strasse 9, Wurzburg D-8700, W. Germany

Adv Exp Med Biol; 136(partA):659-666 1982

39. METABOLIC ACTIVATION AND HEPATOTOXICITY OF TRICHLOROETHYLENE.

Reynolds ES, Moslen MT

Chemical Pathology Lab., Dept. Pathology, Univ. Texas Medical Branch, Galveston, TX

Adv Exp Med Biol; 136(partA):693-701 1982

40. THE ACTIVATING ROLE OF GLUTATHIONE IN THE MUTAGENICITY OF 1,2-DIBROMOETHANE.

van Bladeren PJ, Breimer DD, Rotteveel-Smija GM, Hoogeterp JJ, Mohn GR, De Groot A, Van Zeeland AA, Van der Gen A

Dept. Pharmacology, Univ. Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands

Adv Exp Med Biol; 136(partA):809-820 1982

41. METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS IN PLACENTA.

Juchau MR, Chao ST, Namkung MJ

Dept. Pharmacology, Sch. Medicine, SJ-30, Univ. Washington, Seattle, WA, 98195

Adv Exp Med Biol; 136(partA):555-573 1982

MODIFICATION OF CARCINOGENESIS

42. THE INTESTINAL ENZYMATIC BIOTRANSFORMATION SYSTEM: POTENTIAL ROLE IN PROTECTION FROM COLON CANCER.

Hoensch HP, Hartmann F

Medizinische Universitatsklinik, D-7400 Tubingen, W. Germany

Hepatogastroenterology; 28(4):221-228 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

43. THE ONCOGENIC CIRCLE CLOSES.

Rigby PW

Imperial Coll. Science and Technology, London SW7 2BZ, England

Nature; 297(5866):451-453 1982

44. ANALYSIS OF CASES OF HEPATIC CELL CARCINOMA THAT TRANSFORMED FROM VIRAL HEPATITIS.

Ichida F, Honma A, Soga K

Third Dept. Internal Medicine, Niigata Univ. Sch. Medicine, Niigata, Japan

Nippon Rinsho; 40(2):468-477 1982

In JPN

45. ROLE OF VIRUSES IN THE INDUCTION OF PRIMARY INTRACRANIAL TUMORS.

Walsh JW, Zimmer SG, Perdue ML

Div. Neurosurgery, Univ. Kentucky Medical Center, 800 Rose St., Lexington, KY, 40536

Neurosurgery; 10(5):643-662 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

46. TRANSLATION OF PHARMACOKINETIC/ BIOCHEMICAL DATA INTO RISK ASSESSMENT.

Dietz FK, Reitz RH, Watanabe PG, Gehring PJ

Toxicology Res. Lab., Health and Environmental Sciences, Dow Chemical, 1803 Building, Midland, MI, 48640

Adv Exp Med Biol; 136(partB):1399-1424 1982

47. IN VITRO ASSAYS FOR THE DIFFERENTIATION OF TUMOR PROMOTORS FROM CARCINOGENS AFTER ROUTINE CARCINOGENESIS BIOASSAYS (MEETING ABSTRACT)

Ward JM, Rice JM

Frederick Cancer Research Center, Frederick, MD

Second Annual Meeting of the Society of Environmental Toxicology and Chemistry, November 22-25, 1981, Arlington, Virginia. Society of Environmental Toxicology and Chemistry 150 pp., 1982.

48. ENVIRONMENTAL CARCINOGENS: SELECTED METHODS OF ANALYSIS. VOLUME 4. SOME AROMATIC AMINES AND AZO DYES IN THE GENERAL AND INDUSTRIAL ENVIRONMENT.

Egan H, Fishbein L, O'Neill IK, Castegnaro M, Bartsch H

Lab. Government Chemist, London, England

IARC Sci Publ (40): 347 pp., 1981.

VIDEOTAPES

ON CURRENT TOPICS IN CANCER RESEARCH

A pilot project of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute

Three series are available . . .

THE RELATION OF CARCINOGEN ACTION ON DNA TO CELL TRANSFORMATION

PETER MAGEE Fels Research Institute	*Keynote Address*	#VK01 28 min.
JAMES K. SELKIRK Oak Ridge National Laboratories	*Metabolic Activation and Macromolecular Binding of Chemical Carcinogens*	#VK02 51 min.
PHILIP C. HANAWALT Stanford University	*Cellular Responses to Damaged DNA*	#VK03 54 min.
CHARLES HEIDELBERGER University of Southern California	*Mutagenesis and Oncogenic Transformation of Mouse Embryo Cells*	#VK04 54 min.
FRED RAPP Milton S. Hershey Medical Center	*The Interaction of Herpesviruses and Host Cells Leading to Latency or Transformation*	#VK05 52 min.
	Panel Discussion	#VK06 31 min.

MECHANISMS OF METASTASIS

ISAIAH FIDLER Frederick Cancer Research Center	*The Heterogeneous Nature of Cancer Metastasis and Implications for Therapy*	#VB01 47 min.
GEORGE POSTE Smith, Kline and French Laboratories	*Phenotypic Analysis of Metastatic Cell Populations*	#VB02 42 min.
LANCE LIOTTA National Cancer Institute	*Tumor Cell Invasion of Basement Membranes and Extracellular Matrices*	#VB03 33 min.
EVERETT SUGARBAKER Miami Cancer Institute	*Some Clinical Characteristics of Metastasis in Man*	#VB04 41 min.

AUTOMATED CYTOLOGY

Part One: Principles and Techniques	#VB05 56 min.
Part Two: Biological Applications	#VB06 52 min.

VIDEOTAPES ON CURRENT TOPICS IN CANCER RESEARCH are in the 3/4" U-matic format and can be played on video equipment which accepts the NTSC standard (the standard for videotapes produced in the U.S.). The two Automated Cytology tapes (#VB05 and #VB06) are also available in the PAL format.

The videotapes are available on a loan basis. If you would like to schedule viewing for your group, or for more information, please write to:

Videotape Coordinator
ICRDB Program
Westwood Building, Room 10A18
Bethesda, MD 20205

Please specify three choices for viewing dates, and the tapes desired.

CANCERLINE

More Than Just A Fancy Name

Mention CANCERLINE to your librarian and the world's foremost collection of cancer information is at your disposal. With the help of this computerized data system, you can obtain information on the following:

Cancer Literature

The literature date base, **CANCERLIT**, allows you to survey more than 3,000 biomedical journals for information on your topic of interest. Your search will also alert you to meeting proceedings, monographs, and books published in that area. Informative abstracts averaging 200 words are provided with each citation;

Current Cancer Research

The data base **CANCERPROJ** allows you to retrieve descriptions of current work in any cancer research area. The descriptions, which state research objective, methodology, and experimental results, are supplied for projects underway in 77 countries around the world.

Cancer Therapy Protocols

The **CLINPROT** section of CANCERLINE is designed primarily for clinicians. It provides detailed summaries of currently active experimental protocols for any cancer site, agent, or type.

Ask your biomedical librarian about CANCERLINE.
CANCERLINE is sponsored by the International Cancer Research Data Bank—a program of the National Cancer Institute.

CANCERLINE

Keep Up with the Cancer Literature

Each Month
You Can Receive Abstracts
Covering Your Specialty Area

- This convenient service — called Auto SDI* — is as near as your nearest biomedical library. Discuss your research interests with the librarian who will design an appropriate search strategy.
- Abstracts of the latest published literature are searched automatically each month and those related to your interests are delivered to you on a regular basis.
- The abstracts you receive are selected from more than 4,000 monthly entries made into CANCERLIT — the extensive cancer literature data base of the National Cancer Institute.

Talk With Your Librarian
About the Auto SDI Service TODAY.

*Auto SDI stands for Automatic Selective Dissemination of Information. It is a service provided to you, at minimal cost, by the International Cancer Research Data Bank (ICRDB) — a part of the National Cancer Institute.

☆ U.S. GOVERNMENT PRINTING OFFICE: 1982-381-847:203

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
5285 Port Royal Road
Springfield, Va. 22161

OFFICIAL BUSINESS

Penalty for Private Use, $300

PRINTED MATTER

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF COMMERCE
COM-211

THIRD CLASS
BULK RATE

U.S. MAIL

CK-01

CANCERGRAMS are distributed for the International Cancer Research Data Bank (ICRDB) by the National Technical Information Service (NTIS). CANCERGRAMS are available from NTIS on a standing order basis at $2 each for North American Continent addressees and $3 each for other addressees. An NTIS deposit account is required. For a list of subject categories or other information, please write to:

Subscription Section
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161

NOTICE OF MAILING CHANGE

☐ Check here if you wish to discontinue receiving this publication.

☐ Check here if your address has changed and you wish to continue receiving this publication. (Be sure to furnish your complete address including zip code.)

Tear off cover with address label still affixed and send to:

Computer Support Center
ICRDB Program
IIT Research Institute
10 West 35th Street
Chicago IL. 60616

CK 01/82/12

NCI/ICRDB/CK01 82/12

PB82-935112

ICRDB CANCERGRAM

CHEMICAL CARCINOGENESIS

Nitroso Compounds

SERIES CK01 No. 82/12

DECEMBER, 1982

This Cancergram is a service of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM of the U.S. National Cancer Institute. Every few weeks, an updated Cancergram containing abstracts of selected cancer-related articles recently published in more than 3000 journals, and dealing with the topic indicated by the above title, is sent to researchers working in this area. These researchers are identified on the basis of the description of their current research project that has been submitted to the ICRDB Program, directly or via granting agencies.

This Cancergram is prepared by the Cancer Information Dissemination and Analysis Center (CIDAC) for Carcinogenesis Information. ***If this Cancergram is useful and valuable, please send your comments to the CIDAC address below, since future editions depend on user satisfaction and user needs:***

CIDAC FOR CARCINOGENESIS INFORMATION
SCIENCE INFORMATION SERVICES
FRANKLIN INSTITUTE RESEARCH LABORATORIES
20TH AND RACE STREETS
PHILADELPHIA, PA 19103

NEWARK PUBLIC LIBRARY

DEC - 9 1982

U. S. GOVT. PUB.
DEPOSITORY 376

In this issue:

- **FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS..... 1-3**
- **METABOLISM OF NITROSO COMPOUNDS..... 4-16**
- **INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS..... 17-28**
- **MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS..... 29-42**
- **MUTAGENICITY OF NITROSO COMPOUNDS..... 43-45**
- **CELLULAR EFFECTS OF NITROSO COMPOUNDS..... 46-54**
- **EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS..... 55-57**

FORMATION, SYNTHESIS AND ANALYSIS OF NITROSO COMPOUNDS

1. THE EFFECT OF OXYGEN ON NITROSAMINE FORMATION IN BACON.

Dennis MJ, Massey RC, McWeeny DJ

Food Lab., Ministry Agriculture, Fisheries and Food, Haldin House, Queen St., Norwich NR2 4SX, England

Z Lebensm Unters Forsch; 174(2):114-116 1982

The effect of oxygen on the formation of nitrosamines was studied in samples of bacon during cooking. Cooking the bacon in a nitrogen atmosphere reduced levels of N-nitrosodimethylamine and N-nitrosopyrrolidine in cooking vapors by 50-90%, compared with cooking in air. Results indicate that oxidation of nitric oxide is a key step in the formation of nitrosamines. (8 Refs)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20.3173/2:

2. FORMATION OF N-NITROSONORNICOTINE IN BURLEY TOBACCO MATERIALS DURING CURING AND STORAGE IN CONTROLLED ENVIRONMENTS (MEETING ABSTRACT).

Andersen RA, Oh JH, Kasperbauer MJ
Department of Agronomy, University of Kentucky, Lexington, KY, 40546
Proc Am Assoc Cancer Res; 23:413 1982

Effects of storage (aging) conditions on concentrations of carcinogenic N-nitrosonornicotine (NNN) and probable NNN precursor compounds were determined in experimentally-cured and conventionally air-cured burley tobaccos. Homogenized leaf-cured (HLC) tobacco was prepared by homogenization of ripe green leaves, incubation of the homogenate for 20 hr followed by rapid dehydration of the material. HLC and air-cured tobacco materials were aged at either 8, 12 or 16% moisture levels and 20 or 30 C temperatures for one year. NNN concentrations were 200-300X greater in HLC than in air-cured tobaccos immediately after curing and also throughout the storage period. In addition, NNN concentrations in tobaccos of both curing regimes increased up to a max of 3X after a 52-week storage period. In contrast, concentrations of NNN precursors including total alkaloids, nicotine, nitrate-N and nitrite-N decreased 17-83% in the HLC tobaccos during the storage period, while only nitrate-N and nitrite-N decreased significantly in air-cured tobacco. In general, the rate and magnitude of net change in a component concentration was increased at higher temperature and moisture storage levels. Authentic NNN was investigated by the Sister Chromatid Exchange (SCE) assay using a rat liver S9-activation system. No significant increases in exchange frequencies were observed when human lymphocytes were exposed to NNN at concentrations up to 100 ppm, whereas BP induced a doubling of exchanges at 2 ppm. (no Refs)

3. SYNTHESIS AND EVALUATION OF THE ANTIMITOTIC ACTIVITY OF NITROSOUREAS DERIVED FROM AMINO ACIDS.

Montero JL, Leydet A, Dewynter G, Seguin A, Favre JM, Imbach JL
Laboratoire de Chimie Therapeutique, Faculte des Sciences d'Abidjan, 04 B. P. 322, Adidjan 04 (RCI), France
Eur J Med Chem Chim Ther; 17(3):257-263 1982

The synthesis of 22 nitrosoureas derived from amino acids and one from a dipeptide is described. Antimitotic activity was tested against the growth of the root of Lepidium sativum and in L1210 leukemia in mice. Relationship of antimitotic activity to constituent amino acids is discussed. (19 Refs) (In FRE)

METABOLISM OF NITROSO COMPOUNDS

4. COMPARATIVE METABOLISM OF N-NITROSOBIS(2-OXOPROPYL)AMINE (BOP) IN HAMSTERS AND RATS (MEETING ABSTRACT).

Lawson T, Helgeson AS, Nagel D
Eppley Institute, University of Nebraska Medical Center, Omaha, NE, 68105
Proc Am Assoc Cancer Res; 23:338 1982

BOP induces mostly pancreas tumors in hamsters and colon or prostate tumors in rats. A single dose is effective in hamsters but multiple doses are needed in rats for tumor production. When a dose of BOP, that only produces pancreas tumors (10 mg/kg) was given to hamsters, BOP was concentrated in the pancreas. The max concentrations were 3.7 ng/mg pancreas and 0.6 ng/mg liver. The concentration of N-nitrosomethyl(2-oxopropyl)amine (MOP), the putative proximate carcinogen from BOP, was higher in the pancreas (0.05 ng/mg) than in the liver (0.02 ng/mg). In rats no concentrating effects for BOP or MOP were seen. Rather the metabolism of BOP was directed to the formation of N-nitrosobis(2-hydroxypropyl)amine (BHP) and N-nitroso(2-hydroxypropyl)(2-oxopropyl)amine (HPOP), which are less specific and less carcinogenic than BOP. In rats the max concentrations of BHP and HPOP were 57 and 290 ng/mg, whereas in hamsters they are 18.9 and 20.9 ng/mg. The apparent preferential synthesis of the less carcinogenic metabolites of BOP by rats correlates with the lower carcinogenicity of BOP in rats compared with hamsters. Neither BHP nor HPOP were concentrated in the target tissues when given to hamsters or rats. Also only traces of MOP were found after a single dose of either BHP or HPOP. These results support the idea that MOP is a more proximate carcinogenic form of BOP. (no Refs)

5. ESOPHAGEAL AND HEPATIC MICROSOMAL METABOLISM OF N-NITROSO-METHYLBENZYLAMINE (NMBZA) AND N-NITROSODIMETHYLAMINE (NDMA) IN THE RAT (MEETING ABSTRACT).

Labuc GE, Archer MC
Ontario Cancer Institute, Toronto, Ontario, M4X 1K9, Canada
Proc Am Assoc Cancer Res; 23:311 1982

The metabolism of the rat esophageal carcinogen, NMBzA, and the rat hepatocarcinogen, NDMA, was compared using microsomes prepared from the respective target and non-target tissues. Each compound (5mM) was incubated with microsomes and an NADPH generating system. Hepatic microsomes metabolized NDMA to formaldehyde (dimedone assay), and NMBzA to formaldehyde, benzaldehyde and benzyl alcohol (high performance liquid chromatography assay). The overall rates of metabolism of the nitrosamines were similar. However, hepatic microsomal metabolism of NMBzA at the methylene carbon proceeded at 10 times the rate of metabolism at the methyl carbon. In contrast, microsomes from esophageal mucosa metabolized NMBzA to benzaldelyde and formaldehyde only; benzyl alcohol formation was not detected. The rate of benzaldehyde formation was 100 times that of formaldehyde. The esophageal metabolizing system was exclusively located in the mucosa, and preferentially in the microsomal subcellular fraction. The system exhibited properties typical of a cytochrome P-450 pathway, being NADPH dependent, and being inhibited by CO and SKF 525-A, but was unaltered by either phenobarbitone or 3-methylcholanthrene pretreatment. The results indicate that hepatic microsomes metabolize both compounds to a similar extent. In contrast, esophageal microsomes preferentially metabolize the esophageal carcinogen, NMBzA, and the metabolizing system may thus play a role in determining which chemicals induce tumors in the rat esophagus. (no Refs)

6. CONVERSION OF METHYL-N-AMYLNITROSAMINE (MNAN) BY RAT ESOPHAGUS TO METABOLITIES BEARING THE N-NITROSO GROUP (MEETING ABSTRACT).

Mirvish SS, Smith JW, Issenberg P

Eppley Institute Research Cancer, University Nebraska Medical Center, Omaha, NE, 68105

Proc Am Assoc Cancer Res; 23:328 1982

A possible explanation for MNAN carcinogenesis in rat esophagus is that this organ converts MNAN into proximal nitrosamine carcinogens. Hence 4 esophagi (slit, 0.51 g) or 1 g liver slices from untreated MRC-Wistar rats were incubated (3 h, 37 degrees) in 20 mL Eagle's medium containing 3 or 30 mg/L of MNAN. The medium was filtered, absorbed on Celite, and eluted with 100 mL methylene chloride. This was concentrated to 1 mL and 5-10 uL analyzed by gas chromatography. MNAN eluted at 4.5 min. With 3 mg/L MNAN, esophageal metabolites eluted at 25 (0.79% yield from MNAN), 29 (0.22%) and 35 min (0.43%); liver metabolites eluted at 19 (0.98%), 29 (0.31%) and 35 min (1.42%, largest fraction). With 30 mg/L MNAN, both tissues produced the 25-min metabolite. Hamster esophagus (insensitive to nitrosamine carcinogenesis) showed little MNAN metabolism at 3 mg/L, but hamster liver behaved like rat liver. Urine (48 h) of rats injected with 30 mg/kg of MNAN, analyzed after beta-glucuronidase treatment, showed metabolites eluting at 19, 21, 29 and 35 min, totaling 0.4% of MNAN dose. Urinary metabolites were destroyed by 366-nm UV irradiation, confirming the N-nitroso function, and behaved as neutral compounds on solvent partition. Hence rat esophagus produced MNAN metabolites that were N-nitroso compounds, one of which was organ-specific at a low MNAN level. (no Refs)

7. METABOLISM OF TOBACCO-SPECIFIC NITROSAMINES IN CULTURED HUMAN TISSUES (MEETING ABSTRACT).

Castonguay A, Hecht SS, Hoffmann D, Stoner GD, Schut HA

American Health Foundation, Valhalla, NY, 10595

Proc Am Assoc Cancer Res; 23:333 1982

In previous studies, we found N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in ug amounts in tobacco smoke and in 0.1 ug amounts in the saliva of snuff-dippers. In the present study, we have investigated the metabolism of NNN and NNK in human tissues during 24 hours. Metabolism of NNN (54.3 nmol/ml) by cultured human bronchus (HB, 4 cases) resulted in 5'-carbon hydroxylation, pyridine N-oxidation and trace levels of 2'-carbon hydroxylation. Metabolism in HB, peripheral lung, esophagus, and urinary bladder were qualitatively comparable. In HB (8 cases) carbonyl reduction of NNK (155 nmol/ml) to the less potent carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNA1) was a major metabolic pathway. Successive incubation of the medium with HB and NNK indicated that the carbonyl reductase enzyme was not released into the medium. Pyridine N-oxidation, a deactivation pathway, was observed to occur with NNA1 but not with NNK. Human peripheral lung, esophagus, buccal mucosa, and urinary bladder also metabolized NNK to NNA1. Low levels of alpha-carbon hydroxylation of NNK and NNA1 were observed in all tissues studied. (no Refs)

8. INDUCTION OF NITROSAMINE METABOLISM ENZYMES BY DIET AND CHEMICALS (MEETING ABSTRACT).

Tu YY, Yang CS

Department of Biochemistry, New Jersey Medical School, Newark, NJ, 07103

Proc Am Assoc Cancer Res; 23:313 1982

The liver microsomal dimethylnitrosamine demethylase activity (DMNd) of rats was elevated 4-5 fold by the following treatments: (1) pyrazole injected ip at a dosage of 200 mg/kg body weight for 3-4 days, (2) ethanol present at 15-20% in drinking water for 7-10 days, 3) acetone or isopropanol administered po at a dosage of 2.5 ml/kg in a 25% solution for 1-2 days. The gross cytochrome P-450 content and NADPH-cytochrome c reductase activity were not significantly changed by these treatments. Fasting for 3 days caused a moderate increase in DMNd and a decrease in NADPH-cytochrome c reductase activity, but the DMNd was elevated by preincubating the microsomes with purified NADPH-cytochrome P-450 reductase. Thus, all the above treatments appeared to produce a similar type of alteration of microsomal enzymes. They all caused the appearance of new protein species with molecular weights around 52,000 dal. The induction of this protein was inhibited by treatment with CoCl2 which also inhibited the induction of DMNd. The microsomes from the treated rats showed low Km values, ranging from 0.06-0.12 mM for different treatments, in the dimethylnitrosamine demethylase assay. NADPH-cytochrome P-450 reductase was shown to be an essential component enzyme of both the constitutive and induced DMNd. The results suggest that the above treatments induce specific cytochrome P-450 isozymes which are efficient in catalyzing the metabolism of nitrosamines. (no Refs)

9. ALKYLATION OF GUANINE BY N-PROPYLDIAZONIUM ION. MOLECULARITY IS A FUNCTION OF BOTH NUCLEOPHILE AND ELECTROPHILE (MEETING ABSTRACT).

Scribner JD, Ford GP

Pacific Northwest Research Foundation, Seattle, WA, 98104

Proc Am Assoc Cancer Res; 23:235 1982

It has been reported that n-propyldiazonium ion alkylates N-7 of guanine in rat liver DNA to give 7-n-propylguanine, evidence that this ion reacts bimolecularly, without the formation of carbonium ions. It appeared to us, however, that N-7 of guanine may act as a highly nucleophilic trapping agent, and that weaker nucleophiles, such as O6, would react only with the less selective free carbonium ion. This was tested in vitro and in vivo, and theoretical studies undertaken to explain the results. Treatment of guanosine in water with n-propylnitrosourea gave a 3:1 ratio of O6/7 alkylation products. The only detectable O6 adduct was O(6)-isopropylguanosine, while the only detectable N-7 adduct was 7-n-propylguanosine. (3H)-Di-n-propylnitrosamine was injected into rats, which were sacrificed 12 hr later, and the liver DNA and RNA isolated. Portions of the RNA were digested enzymatically or with 1N HCl. The enzyme digest contained standard adducts, which were reisolated by ethyl acetate extraction and thin layer chromatography. After rechromatography of the standards, the specific activity of O(6)-i-propylguanosine was 7x higher than that of O(6)-n-propylguanosine. The acid digest was chromatographed directly with standards on a high resolution ion-exchange column, with a result like that of Park, et al. Thus we have shown that, while N-7 traps the n-propyldiazonium ion in a bimolecular reaction, O6 reacts predominantly in a manner which permits prior decomposition and rearrangement of the

alkyl group, ie, alkylation of O6 has the properties of a unimolecular reaction. (1 Ref)

10. MODIFICATION OF DEOXYGUANOSINE VIA ALPHA-HYDROXYLATION OF N-NITROSOPYRROLIDINE (MEETING ABSTRACT).

Chung FL, Hecht S
American Health Foundation, Valhalla, NY, 10595
Proc Am Assoc Cancer Res; 23:249 1982

The structures of the DNA adducts formed from cyclic nitrosamines, such as N-nitrosopyrrolidine, have not been elucidated. We studied the reactions of alpha-acetoxy-N-nitrosopyrrolidine (alpha-OAcNPYR) and 4-(N-carbethoxy-N-nitrosamino)butanal (CNB) with deoxyguanosine, catalyzed by porcine liver esterase, in pH 7.0 buffer at 37 C. Under these conditions, alpha-OAcNPYR and CNB are both converted to the intermediate, 3-formylpropyldiazo-hydroxide, the potential ultimate carcinogen of NPYR resulting from metabolic alpha-hydroxylation. Two major deoxyribonucleoside products, A and B, were formed in the reaction of alpha-OAcNPYR or of CNB with deoxyguanosine. A and B were isolated by high performance liquid chromatography (HPLC) and their ultraviolet spectra, desorption chemical ionization mass spectra (M+1, m/e 338), electron impact mass spectra of their trimethylsilyl derivatives (M+, m/e 625), and nuclear magnetic resonance spectra determined. The spectral data indicate that A and B are N-1, N-2 substituted tricyclic deoxyguanosine derivatives. Hydrolysis of A or B gave a product with identical HPLC retention volume as one obtained by incubation of NPYR, rat liver 9000 x g supernatant, and [14C]guanosine or [14C]guanosine monophosphate, followed by hydrolysis. The results of this study contrast to those obtained with acyclic nitrosamines, which give mainly 7-alkylation of guanosine and suggest that the mechanisms by which cyclic and acyclic nitrosamines damage DNA may be quite different. (no Refs)

11. ALKYLATION OF NUCLEAR PROTEINS IN RAT LIVER BY DIETHYLNITROSAMINE.

Letnansky K
Inst. Cancer Res., Univ. Vienna, Borschkegasse 8a, A-1090 Vienna, Austria
Cell Mol Biol; 28(3):353-361 1982

After the injection of N,N-di[1-14C]-ethylnitrosamine into hepatectomized rats incorporation of radioactive label into histone and non-histone proteins of liver nuclei is demonstrated. Differences are observed, however, between the alkylation patterns of nuclear proteins from chromatin enriched in transcriptionally active sequences as compared to inactive chromatin. Although many protein components are alkylated in both fractions, the increased incorporation of ethyl residues into histone H2B and the diminished alkylation of histone H1' of the active sequences are particularly striking. Similarly, H2B is ethylated only in the mononucleosomal fraction of nuclease digests which consists of particles released from actively transcribed sequences. While differences are less pronounced between H1' histones from monomeric and oligomeric particles, clear differences were demonstrated with respect to the incorporation of ethyl residues into certain non-histone proteins. (Author abstract) (58 Refs)

12. METABOLISM OF 6-NITROBENZO(A)PYRENE BY HAMSTER EMBRYO CELLS AND RAT LIVER MICROSOMES (MEETING ABSTRACT).

Tong S, Selkirk JK
University of Tennessee-Oak Ridge Graduate School of Biomedical Sciences, Oak Ridge, TN, 37830
Proc Am Assoc Cancer Res; 23:312 1982

Nitrosarenes are formed during combustion of diesel fuel. Several of these compounds are known mutagens in short-term assay and are therefore suspect as presenting a potential human risk. The metabolism of a suspected environmental contaminant, 6-nitrobenzo(a)pyrene, was studied employing hamster embryonic fibroblasts and hepatic microsomes from 3-methylcholanthrene pretreated rats to compare intact cell metabolism against cell-free systems routinely used in short-term mutagenic assays. Organic solvent-soluble metabolites were separated by high-pressure liquid chromatography. Incubation of 6-nitrobenzo(a)pyrene with hamster embryo cells gave rise to both organic and water-soluble metabolites. When ethyl acetate extract of the extracellular medium was analyzed, a major peak at the dihydroxy region was detected 24 hr after introduction of substrate to cell culture. Small amounts of a phenolic product were also obtained at this time point. Subsequent treatment of remaining aqueous phase with beta-glucuronidase, however, indicated that the majority of the phenol produced had readily been converted to water-soluble glucuronide conjugates. Intracellular metabolites of 6-nitrobenzo(a)pyrene were also detected and comprised mainly of phenolic and dihydroxy products. As a comparison to cellular metabolism, hepatic microsomes were incubated with 6-nitrobenzo(a)pyrene in the presence of NADPH. Microsomal metabolism resulted in the production of one major phenolic metabolite, which was previously found to be conjugated in the cellular system, with minor dihydroxy and quinone products. (no Refs)

13. DEACETYLATION OF 4-(5-ACETYLAMINO-2-FURYL)THIAZOLE TO 1-(4-THIAZOLYL)-3-CYANO-1-PROPANONE BY RAT LIVER TISSUES (MEETING ABSTRACT).

Swaminathan S, Bryan GT
Department of Human Oncology, University of Wisconsin Center for Health Sciences, Madison, WI, 53792
Proc Am Assoc Cancer Res; 23:334 1982

We postulate metabolic reduction of the rat carcinogen 4-(5-nitro-2-furyl)thiazole (NFT) to 1-(4-thiazolyl)-3-cyano-1-propanone (TCP). This may proceed from the nitro to the amino analog through the nitroso and N-hydroxylamino intermediates. Formation of TCP could occur at the stages of either N-hydroxylamino or amino intermediates by furan ring cleavage. To examine if 4-(5-amino-2-furyl)thiazole is a precursor for TCP, a stable model compound, 4-(5-acetylamino-2-furyl)thiazole (AAFT), was synthesized and its chemical identity established by spectroscopic and mass spectral analysis. Incubation with rat liver 10,000 g supernatant preparations resulted in the biotransformation of AAFT as evidenced by a decrease in absorption at 290 nm. Incubation of 14C-labeled AAFT followed by extraction with chloroform:ether (1:1) resulted in the recovery of a major portion (56%) of the radioactivity in the organic phase when the label was at the 2-position of the thiazole ring, while the major amount (82%) of radioactivity was recovered in the aqueous phase when the 1-14C-acetyl group was labeled. The radioactivity from the aqueous phase was extractable into the organic phase following acidification to pH 1, an observation consistent with deacetylation. Furthermore, the deacetylation product exhibited a mass spec-

trum, and retention times in gas and high pressure liquid chromatography, similar to that of synthetic TCP. (no Refs)

14. ELECTRON SPIN RESONANCE STUDY ON THE METABOLISM OF 2-NAPHTHYLAMINE AND 1-NAPHTHYLAMINE IN RAT LIVER MICROSOMES.

Nakayama T, Kimura T, Kodama M, Nagata C
Biophysics Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan
Gan; 73(3):382-390 1982

Incubation of 2-naphthylamine (2-NA) with rat liver microsomes fortified with NADPH resulted in the formation of two types of free radicals which were identified as being due to N-hydroxy-2-naphthylamine and 2-amino-l-naphthol. The former radical was shown to be oxidized further to 2-nitrosonaphthalene radical. Compared with the case of the constitutive microsomes, the amount of the free radicals increased progressively on using the microsomes from methylcholanthrene (MC)-induced or phenobarbital (PB)-induced rats. On the other hand, the amount of the free radical formed from 1-naphthylamine (1-NA) was much less than that from 2-NA, so that the radical structure was not identified unambiguously. The enzymes involved in this case were not induced by either MC or PB. Thus, from the viewpoint of free radical formation, the metabolic patterns of 2-NA and 1-NA are quite different and such different behavior might be correlated with the distinct difference in their carcinogenicities. From the inhibitory effects of carbon monoxide, SKF-525A, alpha-naphthoflavone and 1-(1-naphthyl)-2-thiourea on the free radical formation, it was concluded that both mixed function oxidases (cytochrome P-450s) and mixed function amine oxidase (dimethylaniline monoxygenase) are involved in the metabolism of 2-NA. (Author abstract) (31 Refs)

15. ACTIVATION OF N-OH-AAF BY RAT MAMMARY GLAND PARENCHYMAL CELLS VIA A LIPOXYGENASE-PEROXIDASE ROUTE (MEETING ABSTRACT).

Wong PK, Floyd RA
Oklahoma Medical Research Foundation, Oklahoma City, OK, 73104
Proc Am Assoc Cancer Res; 23:323 1982

The proximate carcinogen, N-hydroxy-2-acetylamino-fluorene (N-OH-AAF) was found to be metabolized into 2-nitrosofluorene (NOF) and N-acetoxy-2-acetylaminofluorene (N-OAc-AAF) by rat mammary parenchymal cells through a peroxidative mechanism. The detection of N-OAc-AAF and NOF as end products by high pressure liquid chromatography (HPLC), the presence of nitroxyl free radical as indicated by electron spin resonance spectroscopy (ESR) and the inhibitory actions of peroxidase inhibitors such as ascorbate and p-aminophenol strongly suggest that peroxidative oxidation is the major route operating in such a system and that neither the acyltransferase nor deacylase route occurs to any appreciable extent. Ram seminal vesicle microsomes also activate N-OH-AAF to NOF. Unlike the prostaglandin synthetase, mammary cell enzymes are not affected by indomethacin or aspirin while lipoxygenase inhibitors, 5,8,11,14-eicosatetraynoic acid (ETYA), gossypol and Fe(III) chelators such as deferoxamine inhibit the cell activity. Externally added arachidonate enhances N-OH-AAF activation. The hydroperoxides generated from exogenous and endogenous arachidonate by the lipoxygenase pathway is believed to be the substrate for the peroxidase activation mechanism. Mammary cells isolated from animals on selenium-supplemented diet are less active than cells from animals on selenium-deficient diet. As selenium was known to inhibit tumor formation on experimental animals, lipoxygenase and peroxidase activities of mammary gland cells appear to be related to mammary carcinogenesis. (no Refs)

16. COMPARISON OF N-HYDROXY-PHENACETIN (N-OH-P) AND N-HYDROXY-2-ACETYLAMINOFLUORENE (N-OH-AAF) METABOLISM BY GUNIEA PIG LIVER MICROSOMAL ENZYMES (MEETING ABSTRACT).

Vaught JB, Glowinski IB, King CM
Michigan Cancer Foundation, Detroit, MI, 48201
Proc Am Assoc Cancer Res; 23:330 1982

In the present studies, guinea pig liver microsomes were sonicated and subjected to gel filtration. The column fractions were analyzed for the following activities: (i) colorimetric determination of N-OH-AAF deacylation (ii) catalysis of binding of radiolabeled N-OH-P and N-OH-AAF to (transfer) tRNA (iii) high performance liquid chromatographic (HPLC) determination of metabolism of N-OH-P and N-OH-AAF. The assays for N-OH-AAF deacylation and N-OH-P binding revealed a single peak of activity (peak I). N-OH-AAF binding activity, however, was catalyzed by two peaks (I and II), peak II having a smaller molecular weight. HPLC analysis revealed that metabolism by peak I resulted in about 80% of the arylhydroxamic acids being deacylated to the corresponding nitroso derivatives, through spontaneous oxidation of arylhydroxylamines. Relatively little metabolism (less than 10%) of N-OH-P or N-OH-AAF to deacylated metabolites occurred in the presence of peak II. The data indicate that N-OH-P and N-OH-AAF are activated to nucleic acid binding metabolites by different mechanisms in this system, which are not reflected in differences in the conversion to deacylated metabolites. Nitroso-phenetole and nitroso-fluorene are known to be direct-acting mutagens, making their detection in a biological system of possible relevance to the carcinogenicity of arylhydroxamic acids. (no Refs)

INDUCTION OF NEOPLASMS BY NITROSO COMPOUNDS

17. THE MORPHOLOGY AND BIOLOGICAL BEHAVIOR OF DIELDRIN AND DIETHYLNITROSAMINE-INDUCED HEPATIC TUMORS IN THE MOUSE, WITH SPECIAL REFERENCE TO MALLORY BODIES: A PUTATIVE MARKER FOR NEOPLASTIC CHANGE.

Meierhenry EF
University of California, Davis, CA
Diss Abstr Int [B]; 42(8):3201-B 1982

Weanling male C57BL/6J, C3H/He and B6C3F1 mice were given either dieldrin in the diet at 10 ppm for 85 weeks or 12 mg of diethylnitrosamine 4 times intraperitoneally. Hepatic tumors induced in C57BL/6J and B6C3F1 mice were generally histologically eosinophilic and ultrastructurally contained increased amounts of smooth endoplasmic reticulum (SER) and mitochondria. Tumors in C3H/He mice were heterogeneous or basophilic and ultrastructurally the clear hepatocytes contained increased amounts of glycogen and lipid with decreased SER. Basophilic cells had increased amounts of rough endoplasmic reticulum (RER) and decreased glycogen and lipid. Hepatocytes in malignant tumors resembled those in benign tumors except for a variable dilation of RER and the occasional presence of basement membrane material in the space of Disse and

the focal presence of microvilli on the lateral cell membrane. Histochemical studies revealed that alkaline phosphatase, adenosine triphosphatase, glucose-6-phosphatase, and glycogen content are useful in differentiating benign and malignant tumors. In addition, succinic dehydrogenase activity varied among the different strains of mice. Mallory bodies (MBs) discovered in hepatic tumors induced by dieldrin were almost exclusively confined to tumor tissue, persisted after the removal of dieldrin from the diet and were present in a transplanted hepatocellular carcinoma growing in a nude mouse. These data suggest that MBs are a marker for neoplastic change in dieldrin-treated mice and are a heritable trait under genetic control. (no Refs)

18. STRUCTURE-SPECIFIC DINITROTOLUENE (DNT) PROMOTION OF INITIATED HEPATOCYTES (MEETING ABSTRACT).

Leonard TB, Lyght O, Popp JA
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
Proc Am Assoc Cancer Res; 23:399 1982

Technical grade DNT (tDNT), containing principally the 2,4-(76%) and 2,6-(20%) isomers, is a potent hepatocarcinogen when fed to male F-344 rats for 1 yr (100% incidence). These studies were designed to assess the promoting activity of 2,4- and 2,6-DNT. Male F-344 rats were initiated with a single dose of diethylnitrosamine (DEN) (150 mg/kg; ip) or saline (controls) then fed either 2,4-DNT (27 mg/kg/day) or 2,6-DNT (10 mg/kg/day) for 12 wk. Promoting activity was quantitated by determining the number of histochemically identifiable gamma-glutamyl transpeptidase positive (GGT+) foci. Feeding 2,4-DNT to DEN initiated animals markedly increased GGT+ foci (546/cm(3)) relative to controls (0/cm(3)). Whereas 2,4-DNT alone had little effect on foci incidence, feeding 2,6-DNT alone significantly elevated the background incidence of GGT+ foci (571/cm(3)). When combined with DEN initiation, 2,6-DNT enhanced the number (867/cm(3)) but not the average diameter of GGT+ foci present. These results, together with previously reported initiation data, support the conclusion that 2,6-DNT is a potent hepatocarcinogen with both initiating and promoting activity. In addition, these data indicate that 2,4-DNT also has hepatic promoting activity which likely contributes to DNT carcinogenesis. In conclusion, the carcinogenic activity of tDNT is largely accounted for by the initiating and promoting activity of 2,6-DNT. (no Refs)

19. INITIATION/PROMOTION ASSAY FOR CHEMICAL CARCINOGENESIS IN RAT LIVER.

Herren SL, Pereira MA, Britt AL, Khoury MK
Health Effects Res. Lab., United States Environmental Protection Agency, Cincinnati, OH, 45268
Toxicol Lett; 12(2/3):143-150 1982

A short-term initiation/promotion bioassay using rat liver was developed and the sensitivity of two protocols to hepatic and nonhepatic chemical carcinogens was investigated. Chemicals tested included acetylaminofluorene (AAF), aflatoxin B1 (AFB1), benzene, benzo(a)pyrene (BaP), diethylnitrosamine (DENA), 7,12-dimethylbenzo(a)anthracene (DMBA), dimethylhydrazine (DMH), dimethylnitrosamine (DMN), N-methyl-N-nitro-N-nitrosoguanidine (MNNG), urethane, aflatoxin B2, and benzo(e)pyrene. Test chemical was administered by gavage either 24 hr after partial (two-third) hepatectomy in the broad-spectrum protocol or 14 days prior to partial hepatectomy in the two-stage procedure. Sodium phenobarbital (500 ppm in drinking water) was administered 1 wk after the test substance; the concentration was lowered to 100 ppm after surgery in the two-stage protocol. After 7 wk of promotion, the rats were killed and liver sections were studied for activity of gamma-glutamyl transpeptidase (GGT) and all GGT-positive foci were counted. AAF, BaP, DENA, DMBA, and DMH exhibited an increase in the incidence of foci when administered after partial hepatectomy compared to their administration before surgery. None of the carcinogens were positive in only one protocol. In the broad spectrum protocol, phenobarbital promoted the response of AAF, AFB1, BaP, DENA, DMH, and DMN. Aflatoxin B2 and benzo(e)pyrene were not detected as carcinogens in either protocol. This bioassay appears to be sensitive to a wide variety of chemical carcinogens. (9 Refs)

20. INVESTIGATION OF THE CARCINOGEN-SPECIFIC NATURE OF GAMMA-GLUTAMYL TRANSPEPTIDASE (GGT)-RICH CELLS CHEMICALLY INDUCED IN HAMSTER BUCCAL POUCH EPITHELIUM (HBPE) (MEETING ABSTRACT).

Bernard D, McPartland K, Hassan M, Solt D
Harvard School of Dental Medicine, Boston, MA, 02115
Proc Am Assoc Cancer Res; 23:211 1982

This study was undertaken to determine whether the chemical induction of GGT stained cells in HBPE is carcinogen-specific and thus likely to be a relevant event in HBPE carcinogenesis. Three known carcinogens and several non-carcinogenic irritants were applied repeatedly over a period of several weeks to the buccal pouches of male syrian hamsters. An attempt was made to maximize the exposure of the mucosa to the various agents without destroying the epithelium. At various intervals whole mounts were prepared for histochemical detection of GGT staining basal cells. Full thickness whole mounts of several sq cm in surface area could be harvested from each animal. Multiple discrete populations of GGT stained cells were detected in whole mounts of HBPE exposed to the potent carcinogens 7-12-dimethylbenz(a)anthracene, N-methyl-N-benzylnitrosamine and N-methyl-N-nitrosourea. GGT stained cells were not detected in whole mounts of HBPE exposed to topical applications of croton oil, 12-O-tetradecanoylphorbol-13-acetate (in acetone, 100 ug per application), acetic acid (25% aq sol), ethylphenylpropiolate (6.6% in acetone), phenol (5% in ethylene glycol), retinol palmitate (10% in oil) or turpentine (50% in oil). These results suggest that the induction of GGT stained cell populations may be a significant event in HBPE carcinogenesis rather than a trivial consequence of cellular toxicity or non-specific irritation. (no Refs)

21. AUTORADIOGRAPHY AND PATHOLOGY STUDIES OF CIS-2,6-DIMETHYLNITROSOMORPHOLINE IN SYRIAN HAMSTERS (MEETING ABSTRACT).

Reznik-Schuller HM
National Cancer Institute-Frederick Cancer Research Facility, Frederick, MD, 21701
Proc Am Assoc Cancer Res; 23:197 1982

DMNM, 2,6-Dimethylnitrosomorpholine, is a powerful pancreatic carcinogen in Syrian golden hamsters, with duct carcinomas developing at a high incidence after chronic administration by gavage. The compound exists as a mixture of the cis and trans isomers. The cis isomer has been shown to be a much stronger pancreatic and liver carcinogen in hamsters than is the trans isomer. We studied the morphology of pancreatic tumors induced by the cis isomer by light and electron microscopy, and followed the sequential development in a serial sacrifice study. To complement our data, we examined the intracellular

sites of binding of [3H]-cis-DMNM and [3H]-trans-DMNM in the target organs by light and electron microscopic autoradiography. Our results suggest that the endoplasmic reticulum of pancreatic acinar cells is the principal site of metabolic activation of both isomers with binding of the cis form being significantly higher. Moreover, our pathogenesis data gives evidence that the pancreatic acinar cell is the origin of the induced duct carcinomas. (no Refs)

22. AUGMENTATION OF CARCINOGENESIS BY N-NITROSOBIS (2-OXOPROPYL) AMINE (NBOP) ADMINISTERED DURING 'S' PHASE IN REGENERATING HAMSTER PANCREAS (MEETING ABSTRACT).

Scarpelli DG, Rao MS, Subbarao V
Department of Pathology, Northwestern University Medical School, Chicago, IL, 60611
Proc Am Assoc Cancer Res; 23:224 1982

The present experiments were undertaken to ascertain the neoplastic potential of acinar cells in hamster pancreas. This was accomplished by administering NBOP to regenerating pancreas when the maximum number of acinar cells are in S phase, as compared to only rare islet and duct cells. Regeneration was induced with ethionine in 30 5-6 week old hamsters. These were divided into 2 groups, which were treated as follows: Group I 30 mg NBOP/kgbwt given at 60 hours of regeneration followed by 10mg/kgbwt/week for 9 weeks; Group II 5 mg NBOP/kgbwt at 60 and 66 hours followed by 10 mg/kgbwt/week for 8 weeks. Three groups of animals consisting of 10 each, with normal pancreas served as controls; Group III received NBOP at doses as scheduled for Group I; Group IV received NBOP at doses as scheduled for Group II; and Group V received 10 mg NBOP/kgbwt/week for 10 weeks. Animals were sacrificed when moribund or at 26-28 weeks. Pancreatic ductal adenocarcinomas were induced in all groups. However, the yield of tumors varied as follows: Grp I, 76%; Grp II, 30%; Grp III, 40%; Grp IV, 20%; Grp V, 27%. In each instance, these were invasive lesions. In many animals neoduct formation was evident in acini. The foregoing is additional support for the notion that under appropriate stimulus (ie), acinar cells can modulate to ductal epithelium and may be involved in the development of ductal adenocarcinoma. (no Refs)

23. EFFECT OF PYRIDOXAL DEFICIENCY ON PANCREATIC DNA DAMAGE AND NODULE INDUCTION BY AZASERINE (MEETING ABSTRACT).

Zarlo J, Roebuck BD, Rutkowski JV, Curphey TJ, Longnecker DS
Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH, 03755
Proc Am Assoc Cancer Res; 23:264 1982

The purpose of this study was to determine whether the effects of azaserine on pancreas are pyridoxal-dependent. For DNA damage studies, weanling rats were fed a pyridoxal deficient diet containing 4-deoxypyridoxine, a pyridoxal antagonist, until deficiency was evident (10-12 days). They were then injected with azaserine 90 min before sacrifice. The deficient rats inhibited almost no pancreatic DNA damage (as determined by alkaline elution) in response to azaserine when compared to saline-treated rats on control diet. A structurally different pancreatic carcinogen, Ndelta-(N-methyl-N-nitrosocarbamoyl)-L-ornithine, caused DNA damage in both deficient and control groups. Distribution studies with 14C-azaserine showed that the absence of DNA damage was not due to the lack of azaserine transport into the pancreases of deficient animals. In another study, rats were treated with 4-deoxypyridoxine prior to a single azaserine treatment. Rats were killed 4 mo after azaserine administration. There was a significant reduction in the number of atypical acinar cell nodules in antagonist-treated animals compared to controls treated with azaserine but not with the antagonist. These results strongly indicate that azaserine metabolism and carcinogenicity are dependent on pyridoxal. (no Refs)

24. ETHYLNITROSOUREA-INDUCED THYROID TUMORS IN RATS.

Ird EA, Smirnova IO
All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(3):68-70 1982

Effect of ethylnitrosourea (ENU: 30 mg/kg, ip) on thyroid carcinogenesis was studied in random-bred albino rats subjected to transplacental exposure to sex hormones. Estrogens and androgen were administered to pregnant females on Days 19, 20, and 21 of gestation, and the ENU was administered to the offspring when they were 16-20 days old or 4-6 mo old. The incidence of spontaneous thyroid tumors (solid and follicular adenomas) was 3%. Transplacental administration of the sex hormones, without administration of the ENU, induced thyroid tumors in 13-15% of the males and in 7-8% of the females; almost all of the rats developed solitary adenomas. ENU administration, without prior administration of sex hormones, induced thyroid tumors in 57% of the immature males and 58% of the immature females. Administration of the sex hormones prior to administration of the ENU did not affect the incidence of ENU-induced thyroid tumors in the immature males (40-50%) but reduced the incidence in the immature females (24-28%). ENU administered alone or in combination with sex hormones did not affect the incidence of thyroid tumors in the mature rats. (8 Refs) (In RUS)

25. LYSOSOMAL ISOZYME PATTERNS IN ETHYLNITROSOUREA-INDUCED BRAIN TUMORS.

Qavi HB, Allen N, Clendenon NR
Div. Biochemical Virology, Texas Medical Center, Houston, TX, 77030
Eur J Cancer Clin Oncol; 18(5):463-469 1982

Isozyme patterns for five acid hydrolases, acid phosphatase (AP), aryl-sulfatase (AS), beta-glucuronidase (beta-Glu), N-acetylglucosaminidase (NAG) and beta-galactosidase (beta-Gal), were studied in isolated lysosomes from ethylnitrosourea (ENU)-induced gliomas and compared with normal and newborn rat brains. With polyacrylamide gel electrophoresis (PAGE), AP was separated into three bands, acidic (A), intermediate (B) and basic (C). In tumors and newborn brains there was a decrease in A and C but a significant increase in B. For NAG the acidic form was elevated by 9-19% in tumors, while newborn brains showed a 19% decrease. Even though the band intensities of beta-Glu in tumors and newborn brains were increased, the relative distribution remained similar to normal brain. With isoelectric focusing, five hydrolases were separated into four to five distinct forms. In ENU-induced gliomas the intensities of all peaks were considerably increased, but in most cases the number of isozymes remained the same. In tumors the isoelectric points were shifted towards the acidic side and smaller peaks in the basic regions merged into more acidic peaks. This effect was especially evident for AP and Gal. In the cases of AS, beta-Glu and NAG, consistently more activity was associated with acidic peaks than with the basic ones. Our data indicates that there is a significant increase in acidic forms

of some of the lysosomal hydrolases studied in ENU-induced brain tumors. (Author abstract) (30 Refs)

26. EXPERIMENTAL HEMATOGENIC METASTASES OF MALIGNANT SCHWANNOMA IN THE RAT.

Mandybur TI, Brunner GD
Dept. Pathology and Lab. Medicine, Univ. Cincinnati, Coll. Medicine, 231 Bethesda Ave., Cincinnati, OH, 45267
Acta Neuropathol (Berl); 57(2/3):151-157 1982

The development, growth patterns and morphology of metastatic schwannomas was studied in adult Lewis rats injected iv with malignant cells from an ethylnitrosourea-induced malignant schwannoma. Groups of 10 rats received doses of 0.1, 0.5, 1.0, 5.0, 10, and 100 x 10(5) cells, respectively. Mortality before day 34 was one each in groups with the lowest doses, and 4, 5 and 10 in those with the highest doses, respectively. Lung metastases developed in all animals in all treated groups, but they varied as to location, form, size and frequency that partly depended upon the cell dose. Lung metastases were in the form of microscopic and macroscopic peripheral subpleural tumors, central peribronchial and perivascular tumors, parenchymal tumors, diffuse intraalveolar infiltrates and intravascular tumor emboli. The variety of metastatic tumors was greater in groups that received the higher cell doses. Metastatic tumors of the pericardium were also found in 36 rats. In 13 rats metastatic tumors occurred in kidney, heart, ovary, adrenal gland, intestine, or skeletal muscles. While more organs became involved as cell dose increased, no tumors developed in the brain. (8 Refs)

27. NO EVIDENCE OF CARCINOGENICITY OF N-NITROSOCIMETIDINE IN RATS (MEETING ABSTRACT).

Habs M, Eisenbrand G, Habs H, Schmahl D
German Cancer Research Center, 69 Heidelberg, W. Germany
Proc Am Assoc Cancer Res; 23:409 1982

Since in vitro formed N-nitrosocimetidine (N-NO-Cim) was shown to be mutagenic, inducing strand breaks and reacting with DNA in vitro, we investigated it for carcinogenicity. Two groups of 40 male Sprague-Dawley rats each received 500 and 50 mg/kg N-NO-Cim, respectively, by gavage twice weekly for one year with subsequent lifetime follow-up. Additional 40 rats were orally given the structurally related carcinogen methylnitro-nitrosoguanidine (MNNG) at weekly doses of 80 mg/kg for 3 months. One hundred animals served as untreated controls. MNNG-treated rats died with carcinomas of the forestomach after a median induction time (MIT) of 226 days. Nineteen untreated rats formed neoplasms, including 7 rats with papillomas of the forestomach (MIT: 534 days). No evidently treatment-related tumors were seen in animals receiving N-NO-Cim. Three rats of the high-dose group and 1 animal of the low-dose group showed papillomas of the forestomach. Further gastrointestinal tumors were not seen. Four other tumors were diagnosed in animals receiving N-NO-Cim. Median survival of both N-NO-Cim-treated groups was reduced (400 and 193 vs 630 days in untreated controls). No evidence of carcinogenicity of N-NO-Cim was seen in this bioassay. (no Refs)

28. BREAST TUMORS INDUCED BY N-NITROSOMETHYLUREA (NMU) OR DIMETHYLBENZ(A)ANTHRACENE (DMBA) IN CASTRATED MALES: ROLE OF HIGH FAT DIET (MEETING ABSTRACT).

Rivenson A, Silverman J, Weisburger J
American Health Foundation, Valhalla, NY, 10595
Proc Am Assoc Cancer Res; 23:275 1982

We attempted to extend the findings of Fingerhut and Veenema on the induction of prostate cancer in gonadectomized male Fischer F-344 rats on 20% and 5% fat diets, utilizing iv dosing with 7,12-dimethylbenz(a)anthracene (DMBA), and also 2',3-dimethyl-4-aminobiphenyl (DMAB), and N-nitrosomethylurea (NMU). No prostate cancers were found in rats held for 68 weeks. However, with NMU and DMAB these gonadectomized male rats had breast cancers in a higher incidence on the 20% fat diet with NMU but not with DMAB. All neoplasms were malignant, with invasion and destruction of neighboring tissues, and presenting histologically mixed glandular and squamous structures, quite distinct from lesions usually seen in females. Similar type of adeno-squamous carcinomas could be seen in tumors of the ear duct (Zymbal glands) and bulbo urethral glands developed in rats given the above carcinogens. The topographic location of the tumors labeled grossly as 'breast tumors' excluded other possible similar glandular structures and also a sweat gland tumor since the rat skin does not contain sweat glands. Other tumors noted after the carcinogens given iv were: bladder, DMAB only; small intestine and colon, NMU and DMAB; lung, DMBA, NMU, and DMAB; sc sarcoma, NMU and DMAB; stomach NMU. Several of these cancers exhibited metastases. None of the tumors noted above were present in controls. In summary, NMU and DMAB induced tumors in a number of sites, but selectively caused mammary gland adenocarcinoma and adenosquamous carcinoma, and Zymbal gland adenoepidermoid carcinoma. (1 Ref)

MODIFICATION OF NITROSO COMPOUND CARCINOGENESIS

29. SYNERGISTIC ACTION OF 13-CIS-RETINOIC ACID (CRA) AND 2,6-DIMETHYLNITROSOMORPHOLINE (DMNM) ON THE INDUCTION OF HEPATIC HEMANGIOMAS AND HEMANGIOSARCOMAS IN SYRIAN GOLDEN HAMSTERS (MEETING ABSTRACT).

Stinson SF, Reznik G, Levitt MH
National Cancer Institute, Frederick Cancer Research Facility, Frederick, MD, 21701
Proc Am Assoc Cancer Res; 23:225 1982

During a study designed to test the effect of CRA on the induction of a broad spectrum of neoplasms induced by DMNM, an increase in the incidence of hepatic hemangiomas and hemangiosarcomas was observed in animals given both CRA and DMNM. Groups of 40 male Syrian golden hamsters were given weekly doses of 0, 40, 80 or 160 mg/kg DMNM for 10 weeks. Twenty animals in each group were dosed ig, and the remainder sc. A duplicate series of hamsters was treated in a similar manner except that they were maintained on a diet supplemented with 160 mg/kg CRA. Twelve animals from each group were necropsied at 15, 25, and 40 weeks (six each from ig and sc dosing regimens). Others were killed when moribund. Results by ig and sc routes were comparable. There

was no significant difference in time related mortality between hamsters receiving or not receiving CRA, although weight gain was less in those given CRA. There was an increase in the number of hamsters with hepatic hemangiomas or hemangiosarcomas with increasing levels of DMNM except in the 160 mg/kg group which had substantial early mortality due to DMNM toxicity. These neoplasms were observed in 43/120 hamsters given CRA and DMNM but in only 5/120 given DMNM alone. No neoplasms were found in 40 hamsters given CRA alone. These results indicate synergistic action of DMNM and CRA in the induction of hepatic hemangiomas and hemangiosarcomas. (no Refs)

30. INHIBITION OF CARCINOGENESIS OF THE RAT MAMMARY GLAND AND MOUSE URINARY BLADDER BY A RETINOID AND AN INDUCER OF INTERFERON SYNTHESIS (MEETING ABSTRACT).

McCormick DL, Becci PJ, Moon RC
Illinois Institute of Technology Research Institute, Chicago, IL, 60616
Proc Am Assoc Cancer Res; 23:354 1982

Retinoids are potent inhibitors of chemical carcinogenesis of the mammary gland and urinary bladder in experimental animals. MVE-2 is a divinyl ether-maleic anhydride copolymer which induces interferon synthesis. These studies were conducted to determine the influence on chemical carcinogenesis of combined administration of MVE-2 and the retinoid N-(4-hydroxyphenyl)retinamide (4-HPR). In the mammary study, virgin female Sprague-Dawley rats received a single iv dose of 20 mg N-methyl-N-nitrosourea per kg body weight. In the bladder study, male C57BL/6 x DBA-2 F1 mice received 8 weekly ig doses of 7.5 mg (4-(butylnitrosoamino)-1-butanol). One week after the final carcinogen treatment, animals in both studies were randomized into groups of 50 as follows: (1) placebo diet (2) 4-HPR, 391 mg/kg diet (3) MVE-2, 25 mg/kg body weight, administered ip in 4 week cycles (3 weeks treatment, 1 week rest) throughout the study (4) MVE-2, 12.5 mg,kg, given as above (5) 4-HPR diet + 25 mg MVE-2/kg (6) 4-HPR diet + 12.5 mg MVE-2/kg. In both studies, 4 HPR (group 2) and the high dose MVE-2 (group 3) treatments resulted in a significant inhibition of carcinogenesis. The low dose of MVE-2 (group 4) was not active in chemoprevention. No synergistic or additive interaction was observed between 4-HPR and MVE-2 at either dose level. These data suggest that either 4-HPR and MVE-2 inhibit carcinogenesis by a common mechanism, or, more likely, that the compounds have an antagonistic activity which precludes an additive or synergistic interaction in cancer inhibition. (no Refs)

31. FAILURE OF PHORBOL ESTER TPA TO PROMOTE GROWTH OF IN VIVO-INITIATED RAT HEPATOCYTES TRANSFERRED INTO A CULTURE SYSTEM.

...ano T, Nomura K, Hino O, Kitagawa T
...pt. Pathology, Cancer Inst. Tokyo, Kami-Ikebukuro 1-37-1, Toshima-ku, Tokyo 170, Japan
Gan; 73(3):354-357 1982

The effect of 12-O-tetradecanoylphorbol-13-acetate (TPA), a potent promoter in epidermal carcinogenesis, on the growth of rat hepatocytes initiated in vivo and transferred into a culture system was investigated. The hepatocytes were isolated by enzymatic perfusion from the rat liver after 12 wk of acetylaminofluorene feeding or 2 to approx 6 wk of diethylnitrosamine treatment. TPA did not show any promotive effect in terms of the number and size of proliferative epithelial cell foci derived from initiated hepatocytes, in contrast to the remarkable effect of phenobarbital, which is a potent promoter in hepatocarcinogenesis. The results suggest the existence of organ or target cell specificity of promoters in the two-stage concept of carcinogenesis. (Author abstract) (16 Refs)

32. INHIBITION OF BIS(2-OXOPROPYL)NITROSAMINE-INDUCED COLON CARCINOGENESIS IN THE RAT DIETARY SELENIUM (MEETING ABSTRACT).

Birt DF, Runice CE, Julius AD, Salmasi S, Ryan W
University of Nebraska Medical Center, Omaha, NE, 68105
Proc Am Assoc Cancer Res; 23:349 1982

Dietary selenium (Se) was fed at levels of 0.1 and 2.0 ppm to MRC rats from 7 weeks of age until termination of the study at 58 weeks of age. Weekly injections of bis-(2-oxopropyl)nitrosamine (BOP) (5 mg/kg body weight, sc) began at 8 weeks of age and continued for the duration of the study. Body weights were not influenced by BOP treatment in either sex, or by Se treatment in males. However female body weights were decreased by feeding 2.0 ppm Se by comparison with 0.1 ppm Se for 50 weeks. Determinations of whole blood Se, and plasma and erythrocyte glutathione peroxidase activity (GSH-Px)- were made at 0, 10, 25 and 50 weeks after BOP treatment began. Blood Se rose with dietary Se at all intervals and plasma GSH-Px rose with dietary Se at 25 and 50 weeks, but neither measurement was influenced by carcinogen treatment. In addition erythrocyte GSH-Px increased with dietary Se at 50 weeks and was decreased after 25 weeks of BOP treatment at the low Se levels. The yield of colon adenocarcinomas was reduced in male rats from 32 in 26 rats in the 0.1 ppm Se group to 17 in 29 rats in the 2.0 ppm Se group. Adenocarcinoma incidences dropped from 50% to 28% in these groups. Colon adenocarcinomas were not induced in rats not treated with BOP or in female rats fed either selenium level and treated with BOP. (no Refs)

33. MODIFICATION OF N-DIETHYLNITROSAMINE-INDUCED CARCINOGENESIS BY CLONIDINE, CAFFEINE, AND ETHANOL.

Gurkalo VK, Zabezhinskii MA
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Eksp Onkol; 4(3):25-29 1982

Roles of adrenergic and cholinergic receptors in the mechanism of chemical carcinogenesis were studied in random-bred male rats. The rats received drinking water containing N-diethylnitrosamine (DENA: 70 mg/liter) for 4 mo. Rats in Group 1 received DENA alone those in Group 2 received DENA in combination with clonidine (0.05 mg/kg, ip), those in Group 3 received DENA in combination with ethanol (2 ml/rat, po), and those in Group 4 received DENA in combination with caffeine (3.5 mg/kg, sc). The animals were sacrificed 6 mo after initiation of the experiment, and growths of esophageal and liver tumors that were induced were determined. Histological examination of neoplastic changes in the esophagus and liver showed that caffeine stimulated the DENA-induced carcinogenesis, while clonidine and ethanol inhibited the carcinogenesis. Therapeutic administration of clonidine produced marked inhibition of the DENA-induced liver tumors. Changes in acetylcholinesterase activity in the brain during the DENA carcinogenesis indicated that the modifying effects of clonidine, caffeine, and ethanol were associated with stimulation and inhibition of the autonomic nervous system. (25 Refs) (In RUS)

34. THE STABILITY AND REGRESSION OF DENA INITIATED FOCI BY PHENOBARBITAL (MEETING ABSTRACT).

Herren SL, Pereira M, Britt AL, Khoury MM
U.S. Environmental Protection Agency, Cincinnati, OH, 45268
Proc Am Assoc Cancer Res; 23:376 1982

An initiation/promotion bioassay in rat liver using gamma-glutamyltranspeptidase (GGTase)-positive foci as the endpoint has been developed to determine the carcinogenic potential of chemicals and environmental samples. These foci are presumed to be precancerous lesions. In an experiment to determine the stability and regression of GGTase-positive foci over time, rats received a 2/3 partial hepatectomy followed 24 hr later by diethylnitrosamine (DENA; 0.3 mmole/kg). The rats then received 500 ppm phenobarbital in the drinking water for 8 wk. After 8 wk, half of the rats were continued on phenobarbital and the other half were taken off phenobarbital. The number and area of GGTase-positive foci present in the liver were determined at various time points after DENA administration. The number of foci/cm2 in the rats taken off phenobarbital promotion initially decreased; although by 56 wk it approached the number present in the rats on continuous promotion. The size of the foci at 56 wk was larger in the rats on continuous promotion. After 81 wk, all 6 of the rats on continuous promotion had liver tumors while only 3 of 6 rats removed from promotion after 8 wk had tumors. Therefore, continuous promotion by phenobarbital not only decreased the latent period for the appearance of foci, but also increased the size of DENA initiated foci as well as the ultimate incidence of liver tumors. (no Refs)

35. INHIBITION OF DEVELOPMENT OF METHYLNITROSOUREA-INDUCED RAT COLONIC TUMORS BY PERORAL ADMINISTRATION OF INDOMETHACIN.

Narisawa T, Sato M, Sano M, Takahashi T
Dept. Surgery, Akita Univ. Sch. Medicine, Hondo 1-1-1, Akita 010, Japan
Gan; 73(3):377-381 1982

The nonsteroid antiinflammatory drug indomethacin, a prostaglandin synthesis inhibitor, inhibited the development of carcinogen-induced large bowel carcinomas in rats. CD-Fischer rats were given carcinogenic pretreatment with intrarectal instillation of 2 mg of methylnitrosourea 3x a wk from the 1st to the 5th wk, in order to produce large bowel tumors. Thereafter, peroral administration of a high or low dose of indomethacin dissolved in drinking water (20 ug or 10 ug indomethacin/ml tap water) for 15 wk was started at the 11th wk, before the tumors developed. At autopsy in the 26th wk just after the completion of the 15-wk treatment, the incidence of developing large bowel tumors was significantly reduced in treated rats, compared to untreated control rats; 17% or 14% vs 67%. However, at autopsy in the 36th wk, 10 wk after cessation of the treatment, the development of tumors in treated rats was significantly increased. Thus, indomethacin inhibited the development of methylnitrosourea-induced large bowel tumors in rats. The effectiveness of peroral administration of indomethacin was comparable to that of intraperitoneal administration. It is postulated that treatment with this drug may effectively prevent the development of large bowel cancer in patients at high risk. (Author abstract) (23 Refs)

36. EFFECTS OF ARGININE ON THE CARCINOGENICITY OF N-METHYL-N-NITROSOUREA (MNU) AND 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) (MEETING ABSTRACT).

Burns RA, Milner JA
Department of Food Science, University of Illinois, Urbana, IL, 61801
Proc Am Assoc Cancer Res; 23:271 1982

Female Sprague-Dawley rats were used to investigate the effects of dietary arginine on the occurrence of mammary tumors induced by DMBA and MNU. Sixty rats were fed either a control 14% casein diet or the same diet supplemented with 5% arginine starting at 36 days of age. At 50 days of age, 30 rats from each treatment were intubated intragastrically with 7.5 mg DMBA in sesame oil. The remaining 30 in each treatment were given MNU (40 mg/kg body weight) via the jugular vein. Mammary tumors were detected by weekly palpation from 5-18 weeks after carcinogen administration. Dietary arginine supplementation did not alter food intake or weight gain. Total palpable mammary tumors for each group increased at a linear rate. For DMBA-treated rats the rate was 8.1 new palpable tumors per week for controls compared to 4.7 for arginine-supplemented rats. The respective rates were 8.9 and 6.8 tumors/week for MNU-treated rats. In DMBA-treated rats the time for 50% of the rats to develop tumors was increased from 9.3 to 12.5 weeks by dietary arginine supplementation, whereas in MNU-treated rats this time was not affected by arginine. Eighteen weeks after DMBA, 23 control and 21 arginine-supplemented rats had tumors and after MNU the corresponding numbers were 27 and 23. The greater inhibition by arginine of DMBA- than MNU-induced tumor formation indicates that arginine may inhibit the activation of procarcinogens (DMBA). (no Refs)

37. EFFECTS OF RAT URINE FRACTIONATED BY MOLECULAR WEIGHT ON URINARY BLADDER CARCINOGENESIS (MEETING ABSTRACT).

Oyasu R, Babaya K, Miyata Y
Department of Pathology, Northwestern University Medical School, Chicago, IL, 60611
Proc Am Assoc Cancer Res; 23:404 1982

The present experiment was conducted to determine whether tumor-enhancing activity exhibited by the whole urine resides in a specific fraction(s) when separated by molecular weight. Normal rat urine after preliminary filtration to remove gross debris was filtered through Amicon Diaflo membranes to obtain two types of filtrate, one at an exclusion level of MW 1,000 and the second at an exclusion level of MW 50,000. These filtrates were tested for tumor-enhancing activity in the heterotopically transplanted rat urinary bladders (HTBs) removed from rats pretreated with the carcinogen N-butyl-N-(4-hydroxybutyl)nitrosamine in drinking water for 4 or 10 weeks. The incidences of cancer in HTBs receiving repeated instillations of the filtrate at MW 50,000 did not differ significantly from those of the HTBs receiving whole urine but were significantly higher than those of the HTBs receiving the filtrate at MW 1,000. In the HTBs which had been exposed to the carcinogen for a longer period of time (10 weeks), the filtrate at MW 1,000, enhanced the bladder tumorigenesis over that of the osmolality control. The results indicate that there may be two classes of tumor-enhancing activity: the first and major one being in the fraction above MW 1,000, and a second one being below MW 1,000. The latter fraction appears to exert its effects only on the cells which are in an advanced stage of carcinogenesis. (no Refs)

38. PROMOTION OF LUNG TUMORS IN MICE.

Witschi HP
Oak Ridge Natl. Lab., Oak Ridge, TN
Proceedings of the EPA/HERL International Symposium on Health Effects of Tumor Promotion, held in Cincinnati, Ohio, October 13, 1981. Available from National Technical Information Service, Springfield, VA, as DE82001498:, 26 pp., 1981.

Several elements of two-stage carcinogenesis apply to the development of lung tumors in mice. At least three agents, identified as promoters, will also enhance tumor formation in lung: phorbol, saccharin, and butylated hydroxytoluene (BHT). The antioxidant BHT is effective only if animals are treated after exposure to an initiating agent. Administration can be delayed up to 5 mo after urethan treatment and still enhance tumor formation. BHT enhances lung tumor formation regardless of its route of administration. The lowest dose required to produce an effect has not yet been determined. in at least one mouse strain, BHT also enhances tumor formation in animals initiated with 3-methylcholanthrene or diethylnitrosamine. No evidence is available yet to show that BHT would enhance tumor development in animals treated with subcarcinogenic doses of an initiating compound. Nor has it been possible to produce more tumors with BHT in mouse strains which have a low spontaneous tumor incidence and respond poorly to urethan. Nevertheless, the data collected on the effects of BHT on mouse lung tumor development have broadened the concept of two-stage carcinogenesis and complement the evidence for initiation-promotion available for other epithelial tissues. (Author abstract)

39. ESTRADIOL PROMOTION OF NEOPLASTIC LESIONS IN THE RAT VAGINA AFTER INITIATION WITH N-METHYL-N-NITROSOUREA (MEETING ABSTRACT).

Sheehan DM, Frederick CB, Branham WS, Heath JE
The National Center for Toxicological Research, Jefferson, AR. 72079
Proc Am Assoc Cancer Res; 23:925 1982

Estrogens share a number of biological properties with tumor promoters, and are reported to promote tumorigenesis in two estrogen target organs, the mammary gland and liver. Since the rat vagina is a well described estrogen target organ, we tested the hypothesis that estradiol (E2) is a tumor promoter for the vagina. Rats (CD) ovariectomized at 60 days of age were randomly assigned one week later to one of four treatment groups: 1) initiator only; 2) multiple initiator; 3) initiator-promoter; and 4) promoter only. The initiator was N-methyl-N-nitrosourea (MNU), a short-lived direct acting carcinogen, administered by vaginal instillation in a single dose of 0.25 mg in 75 ul isotonic phosphate buffer to groups 1 and 3. Group 2 received 4 weekly doses of 0.25 mg MNU. Silastic capsules containing E2 (5 mg/ml in 50 ul sesame oil) were implanted in animals of groups 3 and 4, one week after initiator treatment. Silastic implants provided sustained elevated E2 levels, shown by E2 radioimmunoassay and increased uterine weight. After 16 months, vaginal tumor incidence and type were: group 1, 0/9; group 2, 2/8 (papilloma, squamous cell carcinoma); group 3, 4/9 (polyps); group 4, 0/8. Polyps (2-18 mm) were composed of a fibrovascular stroma covered by squamous epithelium of varying thickness. A number of nonneoplastic lesions (groups 3 and 4) were due to E2 with or without MNU. The statistically significant incidence of polyps and their restriction to only the initiator-promoter group suggests that estrogens can promote tumorigenesis in the rat vagina. (no Refs)

40. GASTRIN PROTECTION AGAINST CHEMICALLY INDUCED GASTRIC ADENOCARCINOMAS IN WISTAR RATS: HISTOPATHOLOGY OF THE GLANDULAR STOMACH AND INCIDENCE OF GASTRIC ADENOCARCINOMA.

Tatsuta M, Yamamura H, Taniguchi H, Tamura H
Dept. Gastrointestinal Oncology, Center for Adult Diseases, Osaka 3 3, Nakamichi I-chome, Higashinari-ku, Osaka 537, Japan
JNCI; 69(1):59-66 1982

The effects of gastrin on the histopathology of the glandular stomach and on the incidence of gastric carcinoma induced by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) were investigated in inbred Wistar (W) rats. Prolonged administration of gastrin after treatment with MNNG significantly reduced the incidence of adenocarcinomas of the glandular stomach. In addition, atypical glandular proliferations were significantly less frequent and were smaller, and the incidence of marked mucosal atrophy was significantly reduced in both the antral and oxyntic gland mucosae. Both atypical glandular hyperplasia and mucosal atrophy are precursors of gastric cancers; prolonged administration of gastrin to rats after treatment with MNNG suppressed development of precursors of gastric cancer and so prevented development of gastric cancers. (Author abstract) (19 Refs)

41. A MORPHOLOGIC AND KINETIC BASIS FOR THE MORE INVASIVE CHARACTER OF MNNG-INDUCED DUODENAL TUMORS FOLLOWING PYLOROPLASTY (MEETING ABSTRACT).

Deschner EE, Salmon RJ
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Proc Am Assoc Cancer Res; 23:201 1982

MNMG (N-Methyl-N'-nitro-N-nitrosoguanidine) was delivered in the drinking water (83 mg/l) to 19 male Wistar rats while 8 served as controls. After 12 weeks treatment, a pyloroplasty was carried out on 9 MNNG treated rats and 3 controls. The remaining 10 MNNG-treated rats and 5 controls received no further treatment. Animals given MNNG and sacrificed 26 weeks later had severe dysplasia in the duodenal mucosa while those given MNNG plus a pyloroplasty had massive invasive adenocarcinomas. Pyloroplasty alone or in combination with MNNG decreased the average number of DNA synthesizing cells per column compared with the values from the respective control or MNNG-treated mucosa. In the carcinogen treated duodenal mucosa, individual long crypt columns were seen with 120-132 epithelial cells and 15% greater numbers of 3HTdR (thymidine) labeled cells than in the adjacent mucosa. However, a 3 fold increase in the number of these hyperactive columns was found in the MNNG plus pyloroplasty group. Moreover in the latter group, 26.5% of the columns were longer (133-238 cells) and contained almost double the number of labeled cells/column seen in the surrounding mucosa (18.1 vs 9.4). The increased severity of the tumors in the pyloroplasty group appears to be related to the greater incidence and enhanced proliferative nature of the hyperactive columns. (1 Ref)

42. REDUCTION OF LETHAL TOXICITY OF CHLOROETHYLNITROSOUREAS BY SUGAR ALCOHOLS WITHOUT LOSS OF ANTITUMOR ACTIVITY.

Tashiro T, Inaba M, Sakurai Y
Cancer Chemotherapy Center, Japanese Foundation for Cancer Res., 1-37-1, Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan
Cancer Chemother Pharmacol; 8(2):183-188 1982

The effects of several sugar alcohols, including mannitol, on the lethal toxicity of 1-(2-chloroethyl)-3-(methyl alpha-D-glucopyranos-6-yl)-1-nitrosourea (MCNU) was investigated. While CD2F1 mice given 50 mg MCNU/kg ip died from toxicity 7-10 days after treatment, pretreatment with sugar alcohols (3,000 mg/kg) one minute or less before MCNU prevented death from acute toxicity. Both po and ip administration of sugar alcohols was effective, although po less so. Mannitol was more protective than sorbitol, especially at lower doses. Mannitol-treated animals showed a faster recovery from myelosuppression compared to animals treated with MCNU only. Sugar alcohol protection did not diminish the antitumor effect of MCNU. With P388 mouse leukemia, neither the growth inhibition of MCNU nor the percentage increase in the lifespan of tumor-bearing mice at the minimum effective dose of MCNU were altered. Mannitol also did not diminish the antitumor effect of MCNU against sc-implanted Lewis lung carcinoma. Sugar alcohols apparently play a role in recovery from the toxic effects of MCNU. (6 Refs)

MUTAGENICITY OF NITROSO COMPOUNDS

43. A CELL-MEDIATED MUTAGENESIS ASSAY FOR DIMETHYLNITROSAMINE IN C3H/10T1/2 CELLS (MEETING ABSTRACT).

Mikles-Robertson F, Heidelberger C
University of Southern California Cancer Center, Los Angeles, CA, 90033
Proc Am Assoc Cancer Res; 23:361 1982

The C3H/10T1/2 mouse embryo fibroblast cell line is widely used as a quantitative system to measure oncogenic transformation and mutagenesis. These cells metabolize a number of chemical carcinogens, such as polycyclic aromatic hydrocarbons, to derivatives that produce cytotoxicity, mutagenicity, and cell transformation. However, these cells are incapable of activating some other classes of carcinogens, such as dimethylnitrosamine (DMN). Hence, an activation system has been developed, with emphasis on DMN. We use primary rat liver hepatocytes, prepared by a modification of the procedure of Jones and Huberman, as the activating system for C3H/10T1/2 target cells. The target cells and the hepatocytes are cocultivated for 24 hr at a target cell to hepatocyte ratio of 1:5; after treatment the cells are reseeded, and 24 hr later the selective agent, ouabain (3 mM) is added. Under these conditions DMN causes a dose-related cytotoxicity and mutagenesis; the relative plating efficiencies of the C3H/10T1/2 cells at 1 mM, 100 uM, and 10 uM DMN were 49%, 48%, and 92% respectively. The mutation frequencies X 10(6) were 116, 70.5, and 36.9. The control value was 2.6. In comparative studies of this cell-mediated activation system with S-9 liver homogenate induced with Aroclor 1254 and with an irradiated epithelial cell line (ML 21) derived from regenerating C3H mouse liver, significant activation of DMN was only achieved with the primary hepatocytes. (1 Ref)

44. MUTAGENICITY OF CARCINOGENS IN CULTURED HUMAN EPITHELIAL CELLS (MEETING ABSTRACT).

Allen-Hoffmann BL, Connell ND, O'Connell T, Rheinwald JG
Sidney Farber Cancer Institute, Boston, MA, 02115
Proc Am Assoc Cancer Res; 23:364 1982

Most human cancers arise from epithelial cells. Difficulty in growing these cells has impeded study of the relationship between chemically induced mutation and carcinogenic alterations in human epithelial cells. We used X-rays, N-methyl-N'-nitro-N'-nitrosoguanidine (MNNG), and 7,12-dimethyl benzanthracene (DMBA) to induce mutations in the hypoxanthine-guanine phosphoribosyl-transferase locus (HPRT) of human keratinocytes. Mutant cells were selected by resistance to 6-thioguanine (TG). In order to measure mutation in feeder layer-dependent human epithelial cells a TGr clone of the Swiss mouse fibroblast line 3T3 (3T3M1) was isolated. With 3T3M1 it is possible to select HPRT- epithelial cells while fulfilling their feeder layer requirement. Using this modified system we report the first successful selection of mutant human epithelial cells. A near-diploid human squamous cell carcinoma line, SCC-13y, and normal diploid human keratinocytes were used to select for induced mutations. HPRT- keratinocytes from Lesch-Nyhan patients were used to optimize selection conditions for normal human keratinocytes whereas a spontaneous mutant of SCC-13y was used to determine optimal expression time, population density and TG concentration for the carcinoma line. Mutagens increased the incidence of mutants 50-to 70-fold. Mutant colonies from a DMBA-treated population of SCC-13y were aminopterin-sensitive and possessed no HPRT activity. Selection of induced mutants from normal human keratinocytes and mesothelial cells is in progress. (no Refs)

45. COMPARATIVE MUTAGENICITY AND TERATOGENICITY IN VITRO OF 2-ACETYLAMINOFLUORENE (AAF), N-ACETOXY-2-ACETYLAMINOFLUORENE (AAAF) AND 2-NITROSOFLUORENE (NF) (MEETING ABSTRACT).

Faustman-Watts EM, Yang HL, Greenaway JG, Juchau MR
Department of Pharmacology, University of Washington, Seattle, WA, 98195
Proc Am Assoc Cancer Res; 23:365 1982

Interest in the interrelationships among the carcinogenic, mutagenic and teratogenic effects of chemicals has increased markedly and these were investigated by examining the mutagenic and teratogenic effects in vitro of AAF and two of its potent mutagenic metabolites. AAF displayed neither mutagenicity nor teratogenicity in the absence of a P-450-dependent monooxgenase system within the concentration ranges tested. Mutagenicity was assessed by measuring back-mutations of Salmonella typhimurium auxotrophs; teratogenicity was assayed with explanted ten-day Sprague-Dawley rat embryos that were cultured for 24 hours in vitro. Addition of a hepatic monooxygenase system (S-9 and cofactors) resulted in the production of prominent neural tube abnormalities as well as marked mutagenicity. AAAF and NF both exhibited potent, direct mutagenic and teratogenic effects in vitro. However, NF was approximately 10-fold more active than AAAF as a mutagen but only slightly more active as a teratogen. Furthermore, AAAF produced principally prosencephalic malformations whereas additions of NF resulted primarily in abnormalities of flexure. Neither of the individual metabolites produced the same teratogenic effects as bioactivated AAF. The results indicated a separation of the mutagenic and teratogenic effects of metabolites of AAF and also demonstrated that other metabolites appear to

be responsible for the observed neural tube abnormalities elicited by biotransformed AAF. (no Refs)

CELLULAR EFFECTS OF NITROSO COMPOUNDS

46. IMPROVED TRANSFORMATION OF C3H10T1/2CL8 CELLS BY DIRECT-AND INDIRECT-ACTING CARCINOGENS (MEETING ABSTRACT).

Nesnow S, Garland H, Curtis G
Carcinogenesis and Metabolism Branch, US Environmental Protection Agency, Research Triangle Park, NC, 27711
Proc Am Assoc Cancer Res; 23:284 1982

C3H10T1/2CL8 cells are transformed by a variety of structurally different chemicals, including polycyclic aromatic hydrocarbons, aromatic amines, and pyrimidines. It has been reported that C3H10T1/2CL8 cells are insensitive to the transforming effects of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) unless the cells are synchronized. This finding is particularly interesting because MNNG mutates C3H10T1/2CL8 cells to ouabain resistance without the need for cell synchrony. Aflatoxin B1 (AFB1) also does not transform C3H10T1/2CL8 cells under conditions described by Reznikoff et al. We report here that oncogenic transformation of C3H10T1/2CL8 cells can be improved by treating asynchronous cultures of cells 5 days after seeding. Benzo(a)pyrene-induced transformation was increased fourfold by this method, compared with treating the cells 1 day after seeding. MNNG produced an average of 1 focus/dish, with 61% of the dishes exhibiting foci, when administered 5 days after seeding. Propane sultone and AFB1 also produced marked transformation responses when administered 5 days after seeding. However, 4-dimethylaminoazobenzene and urethane did not induce transformation when administered either 1 day or 5 days after seeding. With all chemicals examined, clonal cytotoxicity was reduced when they were administered 5 days after seeding. (1 Ref)

47. DETECTION OF CARCINOGENS WHICH INITIATE THE PROCESS OF C3H/10T1/2 CELL TRANSFORMATION (MEETING ABSTRACT).

Boreiko CJ, Abernethy DJ, Frazelle JH
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
Proc Am Assoc Cancer Res; 23:285 1982

It is known that Formaldehyde, N-methyl-N'-nitro-N-nitrosoguanidine and aflatoxin B1 initiate the process of C3H/10T1/2 transformation, producing transformed foci only when treated cells are subsequently exposed to the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA). Studies were conducted to establish whether initiation of transformation is a common consequence of exposure to chemical carcinogens. Cell culture conditions optimal for the detection of initiating agents were determined and the ability of carcinogens to transform or initiate transformation examined. Treatment with cytotoxic concentrations of N-nitrosomethylurea, N-nitrosoethylurea, methylmethanesulfonate and ethylmethanesulfonate followed by continuous exposure to 0.25 ug/ml TPA produced foci in at least 25% of the dishes exposed to the highest concentration of each compound. Foci were generally not observed in dishes exposed to TPA alone or in chemically treated dishes not exposed to TPA. Mitomycin C, 5-fluorodeoxyuridine, amethopterin and 5-azacytidine, alone produced foci in 4-47% of treated dishes and exposure to TPA enhanced focus frequency more than two-fold. In the absence of TPA, 3-methylcholanthrene and benzo(a)pyrene produced foci in 50-100% of treated dishes. TPA caused 50% and 22% reductions in focus formation by 3-methylcholanthrene and benzo(a)pyrene respectively. These studies indicate that some classes of carcinogens function as initiating agents in the standard C3H/10T1/2 transformation protocol and that the presence of TPA can significantly enhance the sensitivity of this system to genotoxic substances. (no Refs)

48. A METHOD FOR AMPLIFICATION OF SENSITIVITY OF THE C3H 10T 1/2 CELL TRANSFORMATION ASSAY (MEETING ABSTRACT).

Schechtman LM, Kiss E, McCarvill J, Gallagher M, Kouri RE, Lubet RA
Microbiological Associates, Bethesda, MD, 20816
Proc Am Assoc Cancer Res; 23:289 1982

Although the 10T 1/2 cells have been shown to be sensitive to a variety of chemical carcinogens, not all genotoxins can be detected using the standard transformation assay of Heidelberger and coworkers. Assay modifications, eg cell synchronization have been found necessary in certain instances to yield the expected response. In order to enhance its sensitivity we have modified the standard 10T 1/2 ('Level I') assay by a procedure designated 'Level II Amplification,' wherein target cells are replated at various times post-treatment for expression of phenotypic transformation. The technique is applicable both in the absence and presence of metabolic supplements, and does not require cell synchronization. It permits amplification of chemically transformed cells which might otherwise go undetected in the originally treated cell population. This procedure has resulted in detectable transformation of 10T 1/2 cells by chemical classes such as alkylating agents (eg N-methyl-N'-nitro-N-nitrosoguanidine), aromatic amines (eg 2-acetyl aminofluorene), nitrosamines (eg diethylnitrosamine), and polycyclic hydrocarbons (eg dibenz(a,h)anthracene), which induce little or no Level I response. Detectable focus transformation is specific for carcinogenic chemicals. No response was observed among untreated cells or those exposed to the non-carcinogens phenanthrene and anthracene, or to solvent vehicles (eg acetone). Moreover, chemicals inducing a Level I response continued to yield a Level II response. (2 Refs)

49. LIMITED REMOVAL OF O6-METHYLGUANINE IN SYRIAN HAMSTER EMBRYO CELLS BY CONCENTRATIONS OF METHYLATING CARCINOGENS THAT INDUCE TRANSFORMATION (MEETING ABSTRACT).

Doniger J, Day R, DiPaolo J
Laboratories of Biology and Molecular Carcinogenesis, National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:292 1982

Excision repair of methylated bases, lethality, host cell reactivation of adenovirus, and neoplastic transformation were studied with Syrian hamster embryo cells (HEC) treated for 1 hr with either N-methyl-N'-nitro-N-nitroso-guanidine (MNNG) or methylnitrosourea (MNU). Transformation and survival were analyzed in a 7 day colony assay. DNA, isolated from confluent cultures treated with 3H-methyl-carcinogen, was acid hydrolized. 3H-methylated bases and total guanine were analyzed using reverse phase high pressure liquid chromatography. Equitoxic doses (55-60% survival) of MNNG (.4 ug/

ml) or MNU (20 ug/ml) induce 1.7-1.8% transformation. No transformation was observed in non-treated cultures. Furthermore, equitoxic doses (85-90% survival) of MNNG (.25 ug/ml) or MNU (10 ug/ml) produced the same level of N7-and O6-methylguanine adducts after 1 hr treatment. When HEC were incubated for 24 hr post MNNG or MNU the level of both N7-and O6-methylguanine per mol guanine was reduced by about one half. Thus HEC have a limited capacity to repair both of these adducts. The survival of MNNG treated adenovirus plaqued on confluent non-treated HEC monolayers was intermediate compared to survival on mer+ or mer- human cells. Mer- cells lack the ability to repair O6-methylguanine. The persistence of O6-methylguanine in MNNG or MNU treated HEC is consistent with the hypothesis that this lesion is relevant to induction of carcinogenesis. (no Refs)

50. ADAPTIVE INCREASE OF O6METHYLGUANINE ACCEPTOR PROTEIN IN HELA CELLS IN RESPONSE TO N-METHYL-N'-NITRO-N-NITROSOGUANIDINE TREATMENT (MEETING ABSTRACT).

Waldstein EA
Biology Department, Brookhaven National Laboratory, Upton, NY, 11973
Proc Am Assoc Cancer Res; 23:24 1982

Methyl-N-nitroso compounds produce O6 methylguanine (O6MeGua) in DNA, an adduct implicated in carcinogenesis. We examined the effect of nontoxic N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) doses on the amount of O6MeGua acceptor protein in exponentially growing HeLa cells. The amount of acceptor in cell extracts was measured by the ability to remove 3H-labeled methyl groups from an exogenous DNA in which 75% of the methyl groups are in O6MeGua. Assays determined either the loss of O6MeGua from DNA or the formation of methylated protein as the result of a stoichiometric transfer of the methyl group to a cysteine moiety of protein. Single exposures of cells for 1 hr to increasing concentrations of MNNG resulted, if assayed immediately after treatment, in a linear decrease of O6MeGua acceptor protein available in the cells, as expected in a stoichiometric reaction. On the other hand, prolonged exposures increase markedly the amount of acceptor activity per cell. At a total concentration of 6.8 uM MNNG a 3 fold increase over the base line level was reached. A further increase of MNNG leads to a linear decline in activity with the same slope per uM as for single doses. The estimated base line number of acceptor molecules per cell is 25,000. The induced activity is stable in vivo for at least 24 hr. (2 Refs)

51. LYMPHOCYTES FROM CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS: ABILITY OF EXTRACTS TO REMOVE O6METHYLGUANINE FROM ALKYLATED DNA (MEETING ABSTRACT).

Setlow RB, Waldstein EA, Cao EH, Miller ME, Cronkite EP
Biology and Medical Departments, Brookhaven National Laboratory, Upton, NY, 11973
Proc Am Assoc Cancer Res; 23:51 1982

O6methylguanine (O6MeGua) is a presumptive mutagenic and carcinogenic product in DNA treated in vivo or in vitro with N-nitroso compounds. Normal human cell lines (mer+) remove 6MeGua from their DNA whereas an appreciable number of tumor and virus transformed cell lines are deficient (mer-) in this respect. We examined the O6MeGua-removing capacity of lymphocytes from 6 patients with chronic lymphocytic leukemia (CLL) and one with polycythemia vera (PV). Unexpectedly lymphocytes from CLL patients, mainly B type, appeared to be super mer+, showing an increased capacity to remove O6MeGua when compared to B type lymphocytes of normal individuals. The activity per cell increases with the WBC and the stage of the disease. Unlike normal lymphocytes, incubation of lymphocytes from CLL patients with or without phytohemagglutinin results in a decrease rather than an increase in activity. The activity from CLL patients, as in normal lymphocytes, acts in a stoichiometric fashion and transfers about 80% of the methyl groups to a cysteine moiety of an acceptor protein. The number of acceptor molecules per cell in lymphocytes of CLL patients is estimated to range between 94,000 and 240,000-4 to 10 fold higher than in normal B type lymphocytes. The estimate for lymphocytes from PV patients is about 40,000 which falls in the range of 14,000-110,000 per cell estimated for unstimulated lymphocytes, mostly T type, of normal individuals. (2 Refs)

52. RELATIONSHIP BETWEEN SPECIFIC DNA BASE METHYLATION AND INDUCTION OF CYTOTOXICITY, SISTER-CHROMATID EXCHANGES AND CHROMOSOME ABERRATIONS IN CHINESE HAMSTER CELLS (MEETING ABSTRACT).

Medcalf AS, Connell JR
Michigan State University, East Lansing, MI, 48824
Proc Am Assoc Cancer Res; 23:256 1982

An investigation into the relationship between specific DNA purine methylation and induction of cytotoxicity, sister-chromatid exchanges (SCE) and chromosome aberrations in Chinese hamsters cells (V79) was carried out. Density-inhibited cells were treated with either N-[14C] methyl-N-nitrosourea (MNUA) or [14C] dimethyl sulphate (DMS) and then incubated in the density-inhibited state for various times before being assayed for the three biological end-points. At equitoxic doses of MNUA and DMS, we observed similar SCE frequencies and similar chromosome aberration frequencies. However, MNUA reacted to a far greater extent than DMS at the O-6 atom of guanine, while both agents produced similar levels of 3-meA (methyladenine) and similar levels of 7-meG (methylguanine). Colony-forming ability, as a function of incubation time, was inversely correlated with 3-meA levels in DNA, particularly during the initial 4-8 hr of post-methylation incubation. A decrease in SCE frequency was observed during incubation after treatment, but no significant variation in chromosome aberration frequency was discernable with length of incubation. The results suggest that monofunctional methylating-agent induced cytotoxicity, SCEs and chromosome aberrations are not primarily a consequence of O6-meG formation in DNA and that cytotoxicity and SCE induction may be more dependent on methylation of the N-3 atom of adenine. No specific adduct could be correlated with induction of chromosome aberrations. (no Refs)

53. THE ALKALINE HYDROLYSIS OF PHOSPHOTRIESTERS IN ALKYLATED MAMMALIAN DNA.

Crathorn AR, Shooter KV
Inst. Cancer Res., Royal Cancer Hosp., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Buckinghamshire HP8 4SP, England
Biochim Biophys Acta; 697(2):259-261 1982

Isolated DNA was alkylated with N-[14C]methyl-N-nitrosourea or N-[14C]ethyl-N-nitrosourea. Sedimentation analysis of the alkylated DNA before and after alkaline hydrolysis was used to determine the number of single-strand breaks intro-

duced by hydrolysis of the triesters. Vacuum distillation from alkylated DNA solutions before and after alkaline hydrolysis was used to determine the numbers of triesters hydrolyzing to the alcohol. (Author abstract) (7 Refs)

54. RELATIONSHIP BETWEEN ANCHORAGE-INDEPENDENT GROWTH AND CYTOCHALASIN B-INDUCED MULTINUCLEATION IN CLONED BHK-21/C13 CELLS AND THEIR CHEMICAL TRANSFORMANTS.

Kamei H
Central Res. Inst., Japan Tobacco and Salt Public Corporation, 6-2 Umegaoka, Midori-ku, Yokohama 227, Japan
Cell Struct Funct; 7(1):61-70 1982

Clones of BHK-21 cells derived from flat colonies, that were selected for their extremely low growth on agar plates (Ag-clones) had low cytochalasin B (CB)-multinucleated cell rates (CB-MCR), whereas parent BHK-21 cells could grow on an agar plate and had high CB-MCR. Many transformants induced in an Ag- clone (L77), after treatment with N-methyl-N'-nitro-N-nitrosoguanidine, retained their ability to grow on an agar plate and most showed increased CB-MCR. The study indicates that anchorage-independent growth and CB-multinucleation are closely related, and that both can be induced simultaneously during chemical transformation. (29 Refs)

EPIDEMIOLOGICAL STUDIES AND PUBLIC HEALTH ISSUES INVOLVING NITROSO COMPOUNDS

55. THE HEALTH EFFECTS OF NITRATE, NITRITE, AND N-NITROSO COMPOUNDS: PART 1 OF A 2-PART STUDY.

National Research Council
Washington, DC
The Health Effects of Nitrate, Nitrite, and N-Nitroso Compounds: Part 1 of a 2-Part Study. Available from National Technical Information Service, Springfield, VA, as PB82-182890:, 534 pp., 1981.

The report contains an evaluation of the health effects of nitrate, nitrite and N-nitroso compounds. The major conclusions of this report are that there is not sufficient evidence to suggest that nitrate and nitrite are carcinogenic in animals, and epidemiological studies are also inconclusive. However, nitrate and nitrite can be converted in foods and in the body to nitroso compounds which are carcinogenic in animals and possibly in humans. The added risk for nitrate and nitrite added to foods is small except in special populations consuming large amounts of cured meats. Vitamins C and E were found to be effective inhibitors of nitrosation. The report recommends reducing human exposure to nitrate, nitrite, and N-nitroso compounds, pursuing research on substitutes for nitrite and on antioxidants (eg, vitamins C and E) that can block nitrosation. (Author abstract)

56. LABORATORY DECONTAMINATION AND DESTRUCTION OF CARCINOGENS IN LABORATORY WASTES: SOME N-NITROSAMINES.

Castegnaro M, Eisenbrand G, Ellen G, Keefer L, Klein D, Sansone EB, Spincer D, Telling G, Webb K
International Agency for Res. on Cancer, Lyon, France
IARC Sci Publ 43: 73 pp., 1982.

A program on methods for destruction of carcinogenic laboratory wastes, including those derived from the N-nitrosamines, is presented. N-nitrosamines considered include N-nitrosodimethylamine, N-nitrosodiethylamine, N-nitrosodipropylamine, N-nitrosodibutylamine, N-nitrosopiperidine, N-nitrosopyrrolidine, N-nitrosomorpholine, and N,N'-dinitrosopiperazine. Possible human health hazards from these compounds are reviewed. Degradation techniques are reviewed. Eight methods of degradation were tested; two were either totally inefficient or of questionable efficiency, and one gave unsatisfactory results. The five remaining methods were recommended for decontamination of media (undiluted N-nitrosamines; spills of aqueous, CH_2Cl_2, or ethanol solutions; aqueous solutions; solutions in CH_2Cl_2, ethanol, or in olive oil; content of petri dishes) or for decontamination of glassware (undiluted N-nitrosamines; aqueous, alcoholic, or oily solutions; CH_2Cl_2). The recommended methods include destruction of N-nitrosamines in laboratory wastes using denitrosation with hydrobromic acid, potassium permanganate, or triethyloxonium salts, destruction of N-nitrosamines in laboratory wastes using nickel-aluminium alloy in potassium hydroxide soln, and decontamination of N-nitrosamine contaminated glassware. Appendices are included of nomenclature and chemical and physical data, and studies of the biological degradation and chemical reactions relevant to degradation of N-nitrosamines. (150 Refs)

57. THE NITROSAMINE HAZARD.

Yonkers AJ
Dept. Otolaryngology, Univ. Nebraska, Omaha, NE
Ear Nose Throat J; 61(7):407-414 1982

Experimental, clinical, and biochemical studies of the possible hazard of nitrosamines in the environment to human populations are reviewed. Nitrosamines are also discussed in relation to occurrence in various foods, possible relationship to cancers in certain geographic, their role as adjuvants, and the function of some blocking agents. (65 Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Abernethy DJ 47
Allen N 25
Allen-Hoffmann 44
Andersen RA 2
Archer MC 5
Babaya K 37
Becci PJ 30
Bernard D 20
Birt DF 32
Boreiko CJ 47
Branham WS 39
Britt AL 19
Britt AL 34
Brunner GD 26
Bryan GT 13
Burns RA 36
Cao EH 51
Castegnaro M 56
Castonguay A 7
Chung FL 10
Clendenon NR 25
Connell JR 52
Connell ND 44
Crathorn AR 53
Cronkite EP 51
Curphey TJ 23
Curtis G 46
Day R 49
Dennis MJ 1
Deschner EE 41
Dewynter G 3
DiPaolo J 49
Doniger J 49
Eisenbrand G 27
Eisenbrand G 56
Ellen G 56
Faustman-Watts 45
Favre JM 3
Floyd RA 15
Ford GP 9
Frazelle JH 47
Frederick CB 39
Gallagher M 48
Garland H 46
Glowinski IB 16
Greenaway JG 45
Gurkalo VK 33
Habs H 27
Habs M 27
Hassan M 20
Heath JE 39
Hecht S 10
Hecht SS 7
Heidelberger C 43
Helgeson AS 4
Herren SL 19
Herren SL 34
Hino O 31
Hoffmann D 7
Imbach JL 3
Inaba M 42
Ird EA 24
Issenberg P 6
Juchau MR 45
Julius AD 32
Kamei H 54
Kasperbauer MJ 2
Kayano T 31
Keefer L 56
Khoury MK 19
Khoury MM 34
Kimura T 14
King CM 16
Kiss E 48
Kitagawa T 31
Klein D 56
Kodama M 14
Kouri RE 48
Labuc GE 5
Lawson T 4
Leonard TB 18
Letnansky K 11
Levitt MH 29
Leydet A 3
Longnecker DS 23
Lubet RA 48
Lyght O 18
Mandybur TI 26
Massey RC 1
McCarvill J 48
McCormick DL 30
McPartland K 20
McWeeny DJ 1
Medcalf AS 52
Meierhenry EF 17
Mikles-Robertso 43
Miller ME 51
Milner JA 36
Mirvish SS 6
Miyata Y 37
Montero JL 3
Moon RC 30
Nagata C 14
Nagel D 4
Nakayama T 14
Narisawa T 35
National Resear 55
Nesnow S 46
Nomura K 31
O'Connell T 44
Oh JH 2
Oyasu R 37
Pereira M 34
Pereira MA 19
Popp JA 18
Qavi HB 25
Rao MS 22
Reznik G 29
Reznik-Schuller 21
Rheinwald JG 44
Rivenson A 28
Roebuck BD 23
Runice CE 32
Rutkowski JV 23
Ryan W 32
Sakurai Y 42
Salmasi S 32
Salmon RJ 41
Sano M 35
Sansone EB 56
Sato M 35
Scarpelli DG 22
Schechtman LM 48
Schmahl D 27
Schut HA 7
Scribner JD 9
Seguin A 3
Selkirk JK 12
Setlow RB 51
Sheehan DM 39
Shooter KV 53
Silverman J 28
Smirnova IO 24
Smith JW 6
Solt D 20
Spincer D 56
Stinson SF 29
Stoner GD 7
Subbarao V 22
Swaminathan S 13
Takahashi T 35
Tamura H 40
Taniguchi H 40
Tashiro T 42
Tatsuta M 40
Telling G 56
Tong S 12
Tu YY 8
Vaught JB 16
Waldstein EA 50
Waldstein EA 51
Webb K 56
Weisburger J 28
Witschi HP 38
Wong PK 15
Yamamura H 40
Yang CS 8
Yang HL 45
Yonkers AJ 57
Zabezhinskii MA 33
Zurlo J 23

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. ASBESTOS CARCINOGENESIS: ASBESTOS INTERACTIONS AND EPITHELIAL LESIONS IN CULTURED HUMAN TRACHEOBRONCHIAL TISSUES AND CELLS.
Haugen A, Harris C
Div. Cancer Cause and Prevention, NCI, Bethesda, MD
Recent Results Cancer Res; 82:32-42 1982

2. REVIEW: ORAL CONTRACEPTIVES AND MENOPAUSAL ESTROGENS IN RELATION TO BREAST NEOPLASIA.
Brzezinski A, Schenker JG
Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel
Isr J Med Sci; 18(4):433-438 1982

3. LIVER DISEASES DUE TO HORMONAL CONTRACEPTIVES.
Lie TS
Chirurgische Klinik und Poliklinik, Universitat, Sigmund-Freud-Str. 25, D-5300 Bonn 1, W. Germany
MMW; 124(20):489-494 1982
In GER

RADIATION CARCINOGENESIS

4. THE WORK OF THE NRPB 1977/80 AND A REVIEW OF THE FIRST 10 YEARS.
National Radiological Protection Board
Natl. Radiological Protection Board, Chilton, Didcot, Oxfordshire OX11 0RQ, England
The Work of the NRPB 1977/80 and a Review of the First 10 Years. Chilton, Didcot, Oxfordshire, National Radiological Protection Board, 70 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

5. ALCOHOL AND CARCINOGENESIS.
Seitz HK, Czygan P, Kommerell B
Schwerpunkt Gastroenterologie, Medizinische Universitatsklinik, Bergheimer Str. 58, D-6900 Heidelberg 1, W. Germany
Leber Magen Darm; 12(3):95-107 1982
In GER

6. ZINC, COPPER, AND MANGANESE IN IMMUNE FUNCTION AND EXPERIMENTAL ONCOGENESIS.
Beach RS, Gershwin ME, Hurley LS
Dept. Internal Medicine, Div. Rheumatology-Clinical Immunology, Univ. Calif., Davis, CA, 95616
Nutr Cancer; 3(3):172-191 1982

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

7. TRENDS IN CANCER INCIDENCE: CAUSES AND PRACTICAL IMPLICATIONS. PROCEEDINGS OF A SYMPOSIUM HELD OSLO, NORWAY, 6-7 AUGUST 1980.
Magnus K
The Cancer Registry Norway, Montebello, Oslo 3, Norway
Trends in Cancer Incidence: Causes and Practical Implications, Proceedings of a Symposium held Oslo, Norway, 6-7 August 1980. Washington, D. C., Hemisphere Publishing Corporation, 446 pp., 1982.

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

8. QUANTIFICATION OF OCCUPATIONAL CANCER.
Peto R, Schneiderman M
Nuffield Dept. Clinical Medicine, Radcliffe Infirmary, Univ. Oxford, Oxford, England
Banbury Rep (9): 756 pp., 1981.

9. NASAL CARCINOMA IN WOODWORKERS: A REVIEW.
Wills JH
Sch. Medicine, Uniformed Services Univ. Health Sciences, 4301 Jones Bridge Road, Bethesda, MD, 20814
JOM; 24(7):526-530 1982

10. AIR POLLUTION AND CANCER. A REVIEW OF EXPERIMENTAL INVESTIGATIONS.
Madsen ES, Nielsen PA, Pedersen JC
(c/o Nielsen), Stigardsvej 2, DK-2900 Hellerup, Denmark
Ugeskr Laeger; 144(23):1719-1721 1982
In DAN

11. AIR POLLUTION AS A RISK FACTOR IN LUNG CANCER.
Vena JE
Dept. Social and Preventive Medicine, State Univ. New York at Buffalo, 2211 Main St., Buffalo, NY, 14214
Am J Epidemiol; 116(1):42-56 1982

12. INHALATION CARCINOGENESIS: AN OVERVIEW.
Chretien J
Hopital Laennec, 42 rue du Sevres, F-75007 Paris, France
Recent Results Cancer Res; 82:1-10 1982

13. THE NITROSAMINE HAZARD.
Yonkers AJ
Dept. Otolaryngology, Univ. Nebraska, Omaha, NE
Ear Nose Throat J; 61(7):407-414 1982

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

14. ONCOGENES OF SPONTANEOUS AND CHEMICALLY INDUCED TUMORS.
Weinberg RA
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
Adv Cancer Res; 36:149-163 1982

15. RELATIONSHIP OF DNA TERTIARY AND QUATERNARY STRUCTURE TO CARCINOGENIC PROCESSES.
Lipetz PD, Galsky AG, Stephens RE
Dept. Radiology, Ohio State Univ., Columbus, OH, 43210
Adv Cancer Res; 36:165-210 1982

16. ROLE OF ENZYMATIC METHYLATION OF DNA IN CELL DIFFERENTIATION AND TRANSFORMATION.
Fedorov NA
Central Res. Inst. Hematology and Blood Transfusion, Moscow, USSR
Eksp Onkol; 4(3):3-11 1982
In RUS

17. HYDROGEN ION DYNAMICS AND CANCER: AN APPRAISAL.
Harguindey S
Dept. Thoracic Surgery and Oncology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Med Pediatr Oncol; 10(3):217-236 1982

MODIFICATION OF CARCINOGENESIS

18. CARCINOGENESIS AND BIOLOGICAL EFFECTS OF TUMOR PROMOTERS.
Hecker E
Inst. Biochemistry, German Cancer Res. Center, Heiodelberg, W. Germany
Carcinogenesis 7: 664 pp., 1982.

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

19. AVIAN LEUKEMIA VIRUSES: ONCOGENESES AND GENOME STRUCTURE.
Graf T, Stehelin D
Inst. Virology, German Cancer Res. Center, In Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
Biochim Biophys Acta; 651(4):245-271 1982

20. HYPERPLASTIC AND NEOPLASTIC ERYTHROPROLIFERATIVE DISEASES INDUCED BY ONCOGENIC MURINE RETROVIRUSES.
Scolnick EM
Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20205
Biochim Biophys Acta; 651(4):273-283 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

21. MOLECULAR EPIDEMIOLOGY AND CARCINOGEN-DNA ADDUCT DETECTION: NEW APPROACHES TO STUDIES OF HUMAN CANCER CAUSATION.
Perera FP, Weinstein IB
Div. Environmental Sciences, Columbia Univ., New York, NY, 10032
J Chronic Dis; 35(7):581-600 1982

22. AN EVALUATION OF ASSAY PROCEDURES FOR DETECTION OF TUMOR PROMOTORS.
Sivak A
(c/o P. H. Lohman) Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 98(3):377-387 1982

23. DNA REPAIR ASSAYS AS TESTS FOR ENVIRONMENTAL MUTAGENS. A REPORT OF THE U.S. EPA GENE-TOX PROGRAM.
Larsen KH, Brash D, Cleaver JE, Hart RW, Maher VM, Painter RB, Sega GA
Environmental Mutagen Information Center, Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 98(3):287-318 1982

24. AN EVALUATION OF THE HOST-MEDIATED ASSAY AND BODY FLUID ANALYSIS. A REPORT OF THE U.S. ENVIRONMENTAL PROTECTION AGENCY GENE-TOX PROGRAM.
Legator MS, Bueding E, Batzinger R, Connor TH, Eisenstadt E, Farrow MG, Ficsor G, Hsie A, Seed J, Stafford RS
Dept. Preventive Medicine and Community Health, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
Mutat Res; 98(3):319-374 1982

25. THE PHYSIOLOGICAL IMPORTANCE OF THE COLONIC MICROFLORA.
Gustafsson BE
Dept. Germfree Res., Karolinska Inst., Box 60 400, S-104 01 Stockholm, Sweden
Scand J Gastroenterol [Suppl]; 17(77):117-131 1982

26. AN ASSESSMENT OF THE ROLE OF MICRODOSIMETRY IN RADIOBIOLOGY.
Goodhead DT
Medical Res. Council Radiobiology Unit, Harwell, Didcot OX11 ORD, England
Radiat Res; 91(1):45-76 1982

OTHER REVIEWS IN CARCINOGENESIS

27. PSYCHOSOCIAL ASPECTS OF CANCER.
Cohen J, Cullen JW, Martin LR
Sch. Social Welfare, Univ. California, Los Angeles, Los Angeles, CA
Psychosocial Aspects of Cancer. New York, Raven Press, 320 pp., 1982.

U.S. GOVERNMENT PRINTING OFFICE: 1982-381-847:205

NEW ONCOLOGY OVERVIEWS ON CARCINOGENESIS

The following are titles of retrospective bibliographies that contain 100-500 selected abstracts of recent cancer research publications on carcinogenesis topics. Additional Oncology Overview titles are also available for the Cancer Diagnosis and Therapy Series and the Cancer Virology/Immunology/Biology Series; these titles will be announced on separate forms for convenient ordering.

NOTE: To receive up to THREE complimentary copies, check the titles desired and return this entire form to the International Cancer Research Data Bank (ICRDB) Program.*

CARCINOGENESIS SERIES:

- ☐ The Role of Dietary Nitrate and Nitrite in Human Carcinogenesis (OK-82/01)
- ☐ Age-Related Factors Which May Predispose to Carcinogenesis (OK-82/02)
- ☐ DDT and Its Metabolites in Carcinogenesis (OK-82/03)
- ☐ Polychlorinated Biphenyls and Polybrominated Biphenyls in Carcinogenesis (OK-82/04)
- ☐ Dioxins and Dibenzofurans in Carcinogenesis (OK-82/05)
- ☐ Short-Term Test Systems for Potential Mutagens and Carcinogens: II. Mutagenicity in Mammalian Cell Culture (OK-82/06)
- ☐ Short-Term Test Systems for Potential Mutagens and Carcinogens: III. In Vitro Transformation (OK-82/07)
- ☐ Short-Term Test Systems for Potential Mutagens and Carcinogens: IV. Unscheduled DNA Synthesis (OK-82/08)
- ☐ Short-Term Test Systems for Potential Mutagens and Carcinogens: V. In Vivo Tests for Chromosomal Damage (OK 82/09)
- ☐ Short-Term Test Systems for Potential Mutagens and Carcinogens: VI. In Vitro Tests for Chromosomal Damage (OK-82/10)
- ☐ Selected Enzyme Markers of Hepatocarcinogenesis: Gamma-Glutamyl Transpeptidase, Glucose-6-Phosphatase, Alkaline Phosphatase, ATPase (OK-82/11)
- ☐ Naturally Occurring Dietary Carcinogens of Plant Origin (OK-82/12)
- ☐ Phorbol Ester Action in Cell Culture (OK-82/13)
- ☐ Mutagens and Carcinogens in Cooked, Smoked, and Charred Foods (OK-82/14)
- ☐ Neurocarcinogenesis (OK-82/15)
- ☐ Excision Repair of DNA Damage: I. Enzymology and Mechanisms of Excision Repair (OK-82/16)
- ☐ The Role of Selected Dietary Factors in Carcinogenesis (OK-82/17)
- ☐ Excision Repair of DNA Damage: II. Human Genetic Defects in Excision Repair**
- ☐ Excision Repair of DNA Damage: III. The Regulation of Excision Repair**
- ☐ Chromatin Alterations Associated with Carcinogenesis**
- ☐ Methodology in Use for the Assessment of Carcinogenic Risk: I. Chemical Agents**
- ☐ Methodology in Use for the Assessment of Carcinogenic Risk: II. Radiation**

*Additional titles may be ordered for a small fee from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, Virginia 22161, U.S.A.

**In press - expected in early 1983.

Return this entire form to:

The ICRDB Program
National Cancer Institute
Westwood Building
Room 10A18
Bethesda, Maryland 20205

Print clearly. This will be your mailing label.

Name: _____

Address: _____

_____

_____

NEW ONCOLOGY OVERVIEWS ON CANCER VIROLOGY/IMMUNOLOGY/BIOLOGY

The following are titles of retrospective bibliographies that contain 100-500 selected abstracts of recent cancer research publications on cancer virology/immunology/biology topics. Additional Oncology Overview titles are also available for the Carcinogenesis Series and the Cancer Diagnosis and Therapy Series; these titles will be announced on separate forms for convenient ordering.

NOTE: To receive up to THREE complimentary copies, check the titles desired and return this entire form to the International Cancer Research Data Bank (ICRDB) Program.*

CANCER VIROLOGY/IMMUNOLOGY/BIOLOGY SERIES:

- ☐ Chalones (OB-82/01)
- ☐ Virus Latency and Oncogenesis (OB-82/02)
- ☐ Cell Hybridization (OB-82/03)
- ☐ Endogenous Polypeptide Growth Factors (OB-82/04)
- ☐ Hepatitis B Virus (OB-82/05)
- ☐ Interferon: Preclinical Studies of Antiviral Activity (OB-82/06)
- ☐ Liposomes (OB-82/07)
- ☐ Mechanisms of Resistance to Methotrexate and Other Folate Antagonists (OB-82/08)
- ☐ Interferon: Preclinical Studies of Anticellular, Antitumor, and Immunomodulatory Activities (OB-82/09)
- ☐ The Biochemistry of Cancer-Related Collagens (OB-82/10)
- ☐ The Role of Proteases in Metastasis (OB-82/11)
- ☐ Monoclonal Antibodies (OB-82/12)
- ☐ Natural Killer Cells (OB-82/13)
- ☐ Mitochondrial Respiration in Tumor Cells and Related Systems (OB-82/14)
- ☐ Tumor-Related Ferritins (OB-82/15)
- ☐ Reverse Transcriptase**
- ☐ The Viral Etiology of Cervical Cancer**
- ☐ Membrane Glycoproteins in Control and Malignant Cells**
- ☐ Endogenous Oncorna Viruses and Genes**
- ☐ DNA Viral Transforming Proteins**
- ☐ Modulation of Cancer by Superoxide Dismutase**
- ☐ Protein Kinases Associated with Growth, Differentiation, and Transformation**
- ☐ Non-Histone Proteins in Control and Malignant Cultured Cells**

*Additional titles may be ordered for a small fee from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, Virginia 22161, U.S.A.

**In press - expected in early 1983.

Return this entire form to:

The ICRDB Program
National Cancer Institute
Westwood Building
Room 10A18
Bethesda, Maryland 20205

Print clearly. This will be your mailing label.

Name: _____

Address: _____

_____

_____

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
5285 Port Royal Road
Springfield, Va. 22161

OFFICIAL BUSINESS

Penalty for Private Use, $300

PRINTED MATTER

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF COMMERCE
COM-211

THIRD CLASS
BULK RATE

U.S.MAIL

CK-01

NOTICE OF MAILING CHANGE

☐ Check here if you wish to discontinue receiving this publication.

☐ Check here if your address has changed and you wish to continue receiving this publication. (Be sure to furnish your complete address including zip code.)

Tear off cover with address label still affixed and send to:

Computer Support Center
ICRDB Program
IIT Research Institute
10 West 35th Street
Chicago IL. 60616

CANCERGRAMS are distributed for the International Cancer Research Data Bank (ICRDB) by the National Technical Information Service (NTIS). CANCERGRAMS are available from NTIS on a standing order basis at $2 each for North American Continent addressees and $3 each for other addressees. An NTIS deposit account is required. For a list of subject categories or other information, please write to:

Subscription Section
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161